SaBTO

Advisory Committee on the
Safety of Blood, Tissues and Organs

PATHOGEN INACTIVATION OF PLATELETS

REPORT OF THE SABTO WORKING GROUP

April 2014

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1. EXECUTIVE SUMMARY AND RECOMMENDATIONS

Remit of the group

Against a background of routine bacterial screening of platelets, low viral risk, and emerging infections, the working group has considered the current evidence to determine whether the introduction of Pathogen Inactivation (PI) of platelets is an appropriate risk reduction measure to be introduced by the UK Blood Services.

Evidence has been reviewed on:-

- Efficacy of current screening programmes for infectious agents
- Regulatory and operational considerations of PI
- Efficacy of PI for relevant bacteria and viruses
- Efficacy and safety of platelets in clinical trials and from haemovigilance data
- Efficacy of PI in preventing graft-versus-host disease
- Cost effectiveness.

Conclusions

1. Bacterial screening has proved highly effective in removing platelets contaminated with pathogenic bacteria from the blood supply. There have been no proven transmissions and one 'near-miss' in over 600,000 units tested. However, it is well recognised that screening early in storage can never be 100% effective.

2. Platelet PI is being adopted to an extent in many countries, but only Switzerland has moved to 100% PI. Two systems are CE marked and being marketed, and can be adopted without further regulatory approvals. It remains unclear how adoption would affect Blood Services licences; this can be worked through with the Medicines and Healthcare products Regulatory Agency (MHRA).

3. These systems could fit into Blood Service operations, but further operational evaluations are necessary. In particular, further work is needed to establish the post-treatment handling of platelets treated by system B with regard to protection from light. The volume loss due to PI is offset by removal of the need to take samples for bacterial screening. PI would allow earlier release of platelets to stock than the current screening model used in NHS Blood and Transplant (NHSBT). It remains advantageous to permit a 7 day shelf life. If manufacturers' claims regarding cytomegalovirus (CMV) and irradiation are accepted (see later sections), there would be considerable operational advantages for the end-to-end blood supply chain.

4. Systems have broadly demonstrated adequate bacterial kill across the range of bacteria relevant to recipients of platelet transfusion. However, there is the potential for breakthrough transmissions, by bacterial strains which are poorly penetrated by the chemicals, by spore formers, or by regrowth after treatment. Further work is planned to examine this potential. It cannot be calculated whether PI is more or less effective than screening. Both are likely to have efficacy close to, but not reaching, 100%. If PI were adopted, screening for bacteria could cease.

5. PI technologies have demonstrated multiple log inactivation of a broad range of viral and non-viral pathogens and relevant model viruses, and there is evidence of a good level of pathogen reduction against most known viruses of accepted current relevance in transfusion microbiology. This translates into increased blood safety.

6. Manufacturers' claims include substitution for CMV screening. PI, coupled with leucodepletion, should provide a sufficiently high degree of assurance to clinicians that CMV antibody screening of platelets could cease.

7. The conclusions above also extend to some other viruses of emerging importance in transfusion microbiology. The demonstrable log reduction is highly dependent on the virus physico-chemical properties, as penetration of the active agent is a prerequisite for inactivation. PI is currently seen as an additional, new line of defence, though there is not yet sufficient evidence to allow universal cessation or modification of donor testing and donor deferral. A phased out approach system for donor deferral due to travel may be an option for the future after individual risk assessments.

8. The clinical sub group considered that there were important advantages with PI platelets regarding its impact on transfusion-transmitted infections. Red cells and plasma are not being considered for PI, therefore transfusion-transmitted infections (TTIs) will remain a pertinent issue. The conclusions below apply to both systems A and B unless otherwise stated. The claims regarding transfusion-associated graft-versus-host disease are accepted. The lack of need for irradiation will be of benefit to the providers and hospitals. Fewer apheresis platelet donors will need to be deferred due to positive bacteriology; this will not impact on pooled platelet donors. The removal of product recalls due to positive screening results will be of benefit to the providers and to hospitals.

9. On current trial and haemovigilance evidence, PI technology does not increase major morbidity or mortality in adults and children and there are no major concerns regarding its safety. However, there are drawbacks with regard to the clinical efficacy of platelets treated by PI. Whilst no major difference in haemorrhagic risk has been demonstrated, increases in platelet counts at 1 and 24 hours are consistently lower than in control platelets. The overall clinical implications are hard to ascertain as specific issues (eg alloimmunisation) have not been subject to robust studies. We estimate that, due to reduced platelet recovery and survival, there is likely to be a 5% increase in demand for platelets with either of the two systems which have been subject to clinical trial. There is sufficient evidence to support a 7 day shelf life for system A; further trial data for system B are awaited.

10. Use of PI in non-haematology patients can be approved by extrapolating data from haematology studies. The lack of data on neonates and children raises the need for post-implementation haemovigilance in this group of recipients. The situation of neonates who require platelet transfusion during phototherapy will need further investigation, although this is not an exception recommended by all manufacturers or applied in other countries.

11. Costs of implementation of the three systems range between £8.0 million per year and £14.6 million per year, compared with current irradiation/bacterial screening costs of £3.8 million per year. Calculations of cost-effectiveness assume between 0 and 5%

increase in demand, a 0.75% reduction in wastage, and percentage apheresis between 20% and 50%. In all combinations of these, the cost per quality adjusted life year (QALY) saved is over £1 million for all three PI systems, significantly above the usual requirement of £25 thousand per Quality Adjusted Life Year (QALY).

Working group observations and recommendations for UK Blood Services

1. Pathogen inactivation technologies for platelets would be suitable to replace bacterial screening, with advantages in allowing earlier issue, lack of recalls and improved stock management.

2. Specifically, pathogen inactivation of platelets using the system from Manufacturer A would potentially be a safe and effective alternative to bacterial screening.

3. Pathogen inactivation of platelets using the system from Manufacturer B is not currently recommended as an alternative to bacterial screening, pending further information from clinical trials to support a 7 day shelf life and on the post-treatment handling of platelets with regard to protection from ambient light.

4. Pathogen inactivation of platelets using the system from Manufacturer C is not currently recommended as an alternative to bacterial screening, due to lack of evidence of clinical effectiveness. (The manufacturers are not marketing this product for sale until further clinical studies have been completed).

5. Further studies of certain bacterial strains should be performed now to gain clarity regarding the limitations of each pathogen inactivation system.

6. Pathogen inactivation technologies A and B provide additional assurance with regard to cytomegalovirus safety (in combination with leucocyte depletion), so if either were implemented, serology testing could cease.

7. It is premature to recommend that any pathogen inactivation system should replace any aspect of current screening for HIV, hepatitis C and hepatitis B.

8. Emerging viral infections, including West Nile Virus and hepatitis E, are likely to be eliminated by pathogen inactivation, but each must be considered individually against each system.

9. Pathogen inactivation technologies A and B can replace irradiation of platelets for the prevention of transfusion-associated graft-versus-host disease.

10. Operational planning should assume an increase in demand for platelets by 5%.

11. There are no clinical groups for whom pathogen inactivated platelets should be withheld, although neonates requiring phototherapy require special risk assessment.

12. Robust haemovigilance systems should be in place before implementation to detect rare complications, particularly for children and infants.

13. Although there are clinical and operational advantages of pathogen inactivation, all systems would add considerable cost to platelet provision at current prices. Operational evaluations and dialogue with manufacturers should continue, to establish how implementation costs could be reduced.

14. Taking account of the evidence presented within this review, UK Blood Services should develop a structure and criteria for evaluating and approving new/existing CE-marked systems to pathogen inactivate blood components. Such criteria will obviate the necessity for further review of specific systems by SaBTO.

Working group recommendation to SaBTO

The driver to recommend pathogen inactivation for platelets, in the absence of systems for red cells/whole blood, would be to provide enhanced safety with regard to bacterial transmission. Clear evidence of overall clinical benefit, however, is not apparent at this time:

- Current bacterial screening, combined with diversion pouches and enhanced skin cleansing, is already providing a high degree of bacterial safety, with no reported case of transfusion-transmitted infection in platelets since 2009
- The limitations of pathogen inactivation with regard to certain strains of pathogenic bacterial species remain to be clarified through further studies
- The estimated increase in demand will increase donor exposure and hence potential risks from complications not reduced by either pathogen inactivation or Platelet Additive Solution
- System benefits, such as removal of irradiation machines and travel deferrals, cannot accrue until there are pathogen inactivation systems suitable for either red cells or whole blood. Under the current circumstances, therefore, the cost-effectiveness of pathogen inactivation remains very low.

For these reasons, implementation of PI of platelets is not currently recommended for the UK Blood Services. The issue should be reviewed again if significant new information becomes available with respect to the issues mentioned above, and/or if costs compared to bacterial screening are significantly reduced.

2. BACKGROUND

SaBTO review of pathogen inactivation to prevent bacterial contamination of platelets (2010)

In 2010, SaBTO undertook a review of PI of platelets. The purpose of the review was to consider whether the process would reduce the number of TTIs associated with platelet transfusions; whether the platelet concentrates would be safe for clinical use; the efficacy of pathogen reduced platelet concentrates, and the cost-effectiveness of introducing such systems.

At that time only one manufacturer had sufficient efficacy and safety data, though all three manufacturers developing systems were considered. Meta-analysis of all trials carried out on pathogen inactivation was not available.

During 2009 the HOVON 82 safety trial was being undertaken in the Netherlands. Some results were made available in autumn 2009 and published in abstract form. The results indicated an increase in bleeding episodes and differences in platelet count increment in the PI arm of the trial. However the HOVON 82 study had not at that stage been published in a peer-reviewed journal.

The group considered that cost-effectiveness was well in excess of the £30,000 per annum threshold and reported that even with the potential benefits, and taking into account potential underreporting of TTIs, PI would still be poorly cost-effective.

Following consideration of the available information, and with specific reference to efficacy, safety, cost-effectiveness and potential ancillary benefits, the review group concluded that PI should not be implemented at that time. This decision was the prompt for NHSBT to introduce bacterial screening in 2011.

It was also agreed that a systematic review of all clinical trials of PI platelets should be performed.

Rationale for reconsideration of pathogen inactivation of platelets

There are several factors which have prompted this review. Firstly, three systems for PI of platelets are now CE marked and two systems are in routine use, at least partially, in a number of countries worldwide. Secondly, further trial evidence has become available regarding the safety and efficacy of PI. There has been a Cochrane systematic review/meta-analysis of clinical studies on pathogen inactivated platelets. This found no evidence of a difference in mortality, ‘clinically significant’ or ‘severe bleeding’, transfusion reactions or adverse events between pathogen-reduced and standard platelets. However, post-transfusion platelet count increments demonstrated better results with standard platelets than with pathogen-reduced platelets[1]. Post-marketing surveillance, although limited to date, has not identified inadequate clinical efficacy as an issue. This is discussed in detail in section 6.

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[1] Butler C, Doree C, Estcourt LJ, Trivella M, Hopewell S, Brunskill SJ, Stanworth S, Murphy MF. Pathogen-reduced platelets for the prevention of bleeding. *Cochrane Database of Systematic Reviews* 2013, Issue 3.

A recent review concluded that, for the technologies available, inactivation of most pathogens is good, except for certain non-enveloped viruses. This review also concluded that data from clinical trials and haemovigilance programmes suggest the observed loss of potency is of little clinical significance, with some technology-specific exceptions. Concerns over adverse toxicological effects or neoantigen formation have not been confirmed for currently licensed products[2].

In general, where pathogen inactivation has been introduced, the driver has been to reduce bacterial contamination. However there are additional potential benefits including removal of the requirement for testing for emerging blood borne infections with low level viraemia, relaxation of travel deferrals/cessation of selective pathogen testing of travellers, and cessation of gamma-irradiation to prevent graft-versus-host disease. These benefits would all lead to easier stock management for Blood Services and hospitals, as well as helping to offset the costs of PI. However, some of these benefits cannot be fully realised until there are systems for PI of red cells or whole blood; these are in development.

The SaBTO working group has therefore sought to consider the current evidence to determine whether the introduction of PI of platelets is an appropriate and relevant risk reduction measure to be introduced by the UK Blood Services. Evidence has been reviewed on:-

1. Efficacy of current screening programmes for infectious diseases
2. Current PI systems available, uptake, and regulatory/operational issues
3. Efficacy of pathogen inactivation for relevant bacteria and viruses
4. Efficacy and safety of platelets in clinical trials and from haemovigilance data
5. Efficacy of PI in preventing transfusion-associated graft-versus-host disease
6. Cost-effectiveness.

It should be noted that evidence on the toxicology of the chemical additives has not been reviewed, as this is outwith the expertise of the group. We considered that this aspect was the responsibility of the regulatory review process, for which manufacturers have had to provide considerable data from standard toxicity and mutagenesis models.

Terms of reference and membership of the working group are shown at Appendix 1.

Related SaBTO recommendation on apheresis platelets: September 2013

In September 2013, SaBTO recommended the removal of the requirement to produce 80% of platelets by apheresis and recommended that platelet additive solution (PAS) should be used for the suspension of platelets. This followed a review of apheresis as a variant Creutzfeldt Jakob disease (vCJD) risk reduction measure.

The impact of the introduction of PAS on bacterial growth and detection has been considered. This is described in section 4.

[2] C. V. Prowse. Component pathogen inactivation: a critical review. Vox Sanguinis. 2013. Volume 104(3), PP183-199.

3. TRANSFUSION-TRANSMITTED INFECTIONS IN PLATELETS

Bacterial contamination of platelets

The potential for components, particularly platelets, to become contaminated by microflora from the donor has always been of concern to the Blood Services. Platelet component transfusion is associated with a significant risk of bacterial contamination and, until recently, was the most common TTI reported in the UK.

Since 1995, there have been 35 confirmed cases of bacterial transmission from platelets reported through haemovigilance (NHSBT/Public Health England in 1995, the Serious Hazards of Transfusion (SHOT) scheme since 1996). In 8 of these events the recipient died. (See Table 1.)

Table 1. Bacterial transfusion-transmitted Infection incidents, UK 1995-2012

Year of transfusion	Apheresis	Pooled	Red cells	Prevention Measure
1995	0	1	0	
1996	0	1	0	
1997	1	1	1	
1998	2	1	1	
1999	0	2	2	
2000	3	4	0	
2001	1	4	0	
2002	0	1	0	
2003	2	1	0	Diversion pouch
2004	0	0	0	
2005	0	2	0	
2006	1	1	0	
2007	0	1	2	Improved technique for arm cleansing
2008	2 (4)*	2	0	
2009	1(2)**	0	1	
2010	0	0	0	
2011	0	0	0	Bacterial screening (NHSBT)
2012	0	0	0	
TOTAL EVENTS	**13**	**22**	**7**	
Outcome in recipients				
Minor morbidity	0	2	1	
Major morbidity	11	16	4	
Death	5	4	2	
Total	16	22	7	

*The 2 apheresis donations were both split to make 2 packs each - all 4 transfused. One donation was associated with or contributed to death in both recipients (only the index death shown)

**There were 4 units associated with the index apheresis pack: transfused into 2 recipients

Contamination is thought to occur most commonly by the introduction of bacteria from the donor skin at the time of venesection, or rarely as a result of low level bacteraemia in the donor (from chronic low grade infection or transient bacteraemia).

Transmissions have been seen from both pooled and apheresis donations (Figure 1), although some countries have suggested that pools carry much higher risk (since there are four venepunctures per dose compared with one for apheresis).

Prevention measures against bacterial contamination

Various measures have been implemented to reduce the risk and incidence of bacterial contamination and transmission. In 2003, a diversion pouch was introduced to blood donation collection packs. The diversion pouch diverts the first 20-30 ml of donor blood into a sample pack; the blood is used for routine laboratory tests. In theory, bacteria which may enter the collection system from the skin plug during venepuncture would then be diverted away from the main pack and would not contaminate the final component. There is evidence that the first aliquots of collection do carry a high level of bacterial contamination. This measure alone was predicted to reduce the risk of contamination by 40 – 88%[3]. In 2007, an improved method and technique for donor arm cleansing was introduced to reduce the levels of bacteria present on the donors' skin prior to venepuncture. The method uses 70% isopropyl alcohol with 2% chlorhexidine gluconate applied with an abrasive sponge. There is incontrovertible evidence from studies using contact plates of its effectiveness for arm cleansing prior to venepuncture[4].

In parallel with the improved collection methods, education has been ongoing within Blood Services and hospitals to improve inspection of platelet packs for clumping. This vigilance has prevented transfusion of contaminated and potentially contaminated platelet components. Hospital communications also encourage reporting any suspected bacterial transmission to the Blood Services for investigation.

An additional risk reduction measure is bacterial screening which, although in use in some UK Blood Services earlier, was not introduced in NHSBT until 2011. Therefore there is good data available on the species and frequency of isolation from platelets. An added benefit of bacterial screening was that it allowed the platelet shelf life to be extended from 5 to 7 days. Bacterial screening is discussed in detail later in this paper.

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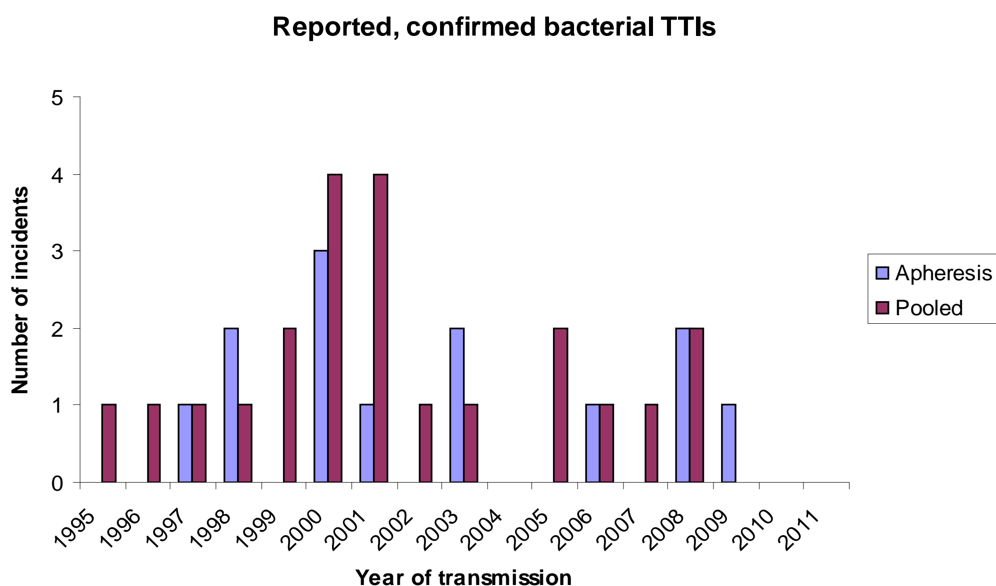
[3] McDonald et al, Vox Sanguinis (2004) 86, 178 - 182

[4] Prevention of healthcare-associated infections in primary and community care. London (UK): National Institute for Clinical Excellence (NICE); Jun 257 p. (292 references)

Figure 1. Surveillance of bacterial TTI's in the UK 1995-2012



There were no reported confirmed bacterial TTIs from platelets or red cells during 2010, 2011 and 2012

Frequency of non-bacterial transfusion-transmitted infections

The transmission of viruses by any component is now rare in the UK due to improvements in donor selection criteria, improved screening tests with shorter window periods and additional processing such as leucodepletion. The last HIV transmission was reported in 2002 and the last hepatitis C (HCV) transmission in 1997[5]. During 2012 the SHOT report [6] confirmed a hepatitis B (HBV) transmission from fresh frozen plasma and a red cell unit, a transmission of parvovirus B19 from a red cell unit and transmission of hepatitis E (HEV) from a unit of fresh frozen plasma. Prior to 2012 there had been no reports of confirmed viral TTIs since 2005. Only occasional viral infections are associated with platelets.

[5] PHE supplementary tables http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139902119 (accessed 05/11/13)

[6] SHOT report 2012 http://www.shotuk.org/wp-content/uploads/2013/08/SHOT-Annual-Report-2012.pdf (accessed 05/11/13)

Table 2. Non-bacterial TTI incidents associated with platelets, UK 1996-2012

Non-bacterial TTI incidents associated with platelets, UK 1996-2012					
Yr of transfusion	**Pooled**	**Apheresis**	**Not known**	**Organism**	**Outcome**
1996			1	HIV	Major morbidity
1997					
1998					
1999	1			HBV	Major morbidity
2000	1			HAV	Major morbidity
2001					
2002					
2003		1		HBV	Major morbidity
2004					
2005	1			HAV	Minor morbidity
2006					
2007					
2008					
2009					
2010					
2011					
2012					
TOTAL	**3**	**1**	**1**		
Outcome					
Minor morbidity	1				
Major morbidity	2	1	1		
Death	0	0			

Table 3. Platelet type, microorganism and outcome of transfusion-transmitted infection, 1995-December 2012

	Microorganism	Apheresis	Pooled	Death	Major morbidity	Minor morbidity
	B. cereus	0	5	1	4	0
	Group B streptococci	0	3	0	3	0
	CNS	0	1	0	1	0
	E. coli	3	0	2	1	0
	S. aureus	2	1	1	2	0
	S. epidermidis	2	9	1	9	1
	K. pneumoniae	1	1	2	0	0
	S. pneumoniae	1	0	0	1	0
	S. bovis	1	0	0	1	0
	S. dysgalactiae	1	0	0	1	0
	Enterobacter cloacae	0	1	0	0	1
	Enterobacter aerogenes	1	0	1	0	0
	Lancefield Group G Streptococci	0	1	0	1	0
	Morganella morganii	1	0	0	1	0
	Total	13	22	8	25	2

Table 4. TTI data

Microorganism and age of platelet at time of transmission, 1995-2012

Microorganism	Age of platelet						
	2 days	3 days	4 days	5 days	6 days	Not known	Total
B. cereus	0	0	4	0	0	1	5
Group B streptococci	0	1	1	0	0	1	3
CNS	0	0	0	1	0	0	1
E. coli	1	1	0	0	0	1	3
S. aureus	0	0	1	1	0	1	3
S. epidermidis	1	0	2	7	1	0	11
K. pneumonia	0	2	0	0	0	0	2
S. pneumo	0	1	0	0	0	0	1
S. bovis	0	1	0	0	0	0	1
S. dysgalactiae	0	0	1	0	0	0	1
Enterobacter cloacae	0	1	0	0	0	0	1
Enterobacter aerogenes	0	1	0	0	0	0	1
Lancefield Group G Streptococci	0	0	1	0	0	0	1
Morganella morganii	0	0	0	1	0	0	1
Total	2	8	10	10	1	4	35

Current bacterial screening programmes in the UK

The bacterial screening programmes currently in use have proven efficacy in identifying platelet packs contaminated with bacteria. All of the UK Blood Services use a bacterial culture method, BacT/ALERT, for bacterial screening, but with slightly differing protocols regarding pre-sampling hold-times, culture volume etc. However, it is accepted that, whatever the method, no bacterial screening system involving sampling early in the shelf life can provide 100% protection against clinically significant bacteria. The major issue is that bacterial contamination of platelets is generally at a very low level, and thus there is a possibility that the sample taken from the platelet pack for culture will contain no bacteria, despite there being a clinically significant inoculum in the pack. Since testing was introduced across the UK, there have been no confirmed bacterial transmissions from platelets, although there was a recent significant 'near-miss' episode (see below). Generally, platelets are held for a specified time after collection before sampling, in order to maximise bacterial multiplication and hence the chances of the sample actually containing bacteria. Samples are then cultured, and released to stock as 'negative-to-date' at a specific time point (6 hours in NHSBT) after the start of culture. Results are transmitted to the manufacturing computer system, which allows issue of components as 'negative to date'. However, the culture is continued till the end of shelf life, allowing recall of any donations which become positive. Table 5 provides an overview of UK bacterial screening strategies. Table 6 provides a summary of screening data across the four UK Blood Services.

Table 5. UK Blood Services bacterial screening sampling and testing strategies

Method	NHSBT	SNBTS[1]	WBS[2]	NIBTS[3]
Minimum time between donation and platelet sampling (hours)	36	18	16	48
Negative- to-date release (hours)	6	6	Available once screening begins	6
Sample volume and incubation conditions	2 x 8 ml aerobic/anaerobic	7 ml aerobic	2 x 10 ml aerobic/anaerobic	2 x 8 ml aerobic/anaerobic
Sampling of apheresis platelets	Each split	Prior to splitting	Prior to splitting	Prior to splitting
Shelf life	7 days	5 days	7 days*	7 days
Incubation period	Till end of shelf life	Till end of shelf life	Till end of shelf life	9 days

* from March 2010 packs have been sampled on day 4, 10 ml aerobic sample, to extend shelf life to 7 days

[1] Scottish National Blood Transfusion Service. Dr Lisa Jarvis personal communication 19/11/13

[2] Welsh Blood Service. http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con149750.pdf

[3] Northern Ireland Blood Transfusion Service. Dr Kathryn Maguire personal communication 19/11/13

Table 6, Summary of bacterial screening data across the four UK Blood Services

	Apheresis Platelets			Pooled Platelets		
Blood Service	Number screened	Initial Reactive	Confirmed Positive (% total)	Number screened	Initial Reactive	Confirmed Positive (% total)
NHSBT 2012	237,212	1,024	36 (0.02)	40,863	128	30 (0.07)
SNBTS 2012	11,940	22	2 (0.02)	4,367	6	1 (0.02)
WBS February 2003-March 2010	17,235	Total* 257	7 (0.04)	37,594		31 (0.08)
NIBTS 2012	3,718	Total 12	0 (<0.01)	1,235		0 (<0.01)

*Total number of both apheresis and pooled platelet packs initially reactive

NHSBT, SNBTS and NIBTS source: data supplied by relevant blood service. WBS source Pearce et al Screening of platelets for bacterial contamination at the Welsh Blood service Transfusion medicine 2011 21, 25-32

NHSBT bacterial screening data

NHSBT introduced bacterial screening of platelet packs in February 2011 and by July 2011 all pooled and apheresis platelets were routinely screened. Units are issued as negative to date more than 42 hours post donation, with a shelf life of 7 days.

The last reported and confirmed bacterial TTI was reported in 2009. A total of 498,801 apheresis packs and 93,051 pooled platelets have been screened to the end of August 2013. Of those packs screened, 159 were confirmed as containing bacteria (0.03%). In addition there were 228 (0.04%) where bacteria were isolated from the initial screening sample but this could not be confirmed either because no platelet pack was available or there was no growth from the index or associated pack.

Table 7. NHSBT cumulative bacterial screening initial reactive and confirmed positive rates 2011-13

	No. screened	No. initial reactive	% initial reactive	No. confirmed positive	% confirmed positive
Apheresis	498,801	2,485	0.5	87	0.02
Pooled	93,051	341	0.37	72	0.08
Total	**591,852**	**2,826**	**0.48**	**159**	**0.03**

Of 159 confirmed positive packs from apheresis and pooled donations, 33 different species were identified (Table 6).

Table 8. Microorganisms isolated through bacterial screening by NHSBT between February 2011 and June 2013; frequency and type of microorganisms

	Apheresis		**Pool**	
Microorganism	**CP**	**IP**	**CP**	**IP**
Skin, Gram-positive rods eg Propionibacteria	32	107	45	24
Skin Gram-positive cocci	15	36	16	22
Oropharyngeal eg oral streptococci	19	13	0	1
Environmental		17	1	6
Significant microorganisms				
Staphylococcus aureus	5	-	2	-
Streptococcus pneumoniae	3			
Streptococcus dysgalactiae spp.	1		5	1
Serratia marcescens	2			
Bacillus cereus				1
Klebsiella pneumoniae	1		1	
Listeria monocytogenes	3			
Streptococcus bovis II	3		1	
Enterococcus faecalis			1	
Campylobacter lari	1			
Escherichiae coli	2			

CP: confirmed positive; IP: indeterminate positive
CP: positivity in one or more tests and a speciation match in the index bottle and platelet pack.
IP: positivity and organisms isolated from either the index bottle or pack but not both - in most cases the initially reactive bottle was positive but the index pack was not available for culture because it had been transfused.

Implications of continuing screening cultures until platelet outdate: the problem of recalls

Where reactive screens are identified after the 6 hour hold period, components are recalled from blood centres or hospitals both to prevent transfusion and for confirmation of the result. For apheresis-derived platelets, this requires all doses produced from the donation to be recalled (the mean number of separate platelet components produced from each donation within NHSBT was 2.14 during 2012). For pooled platelets, the platelet component is recalled and additionally the 4 red cell units associated with the buffy coats used to produce the pooled platelet are also recalled.

Clearly, there is a theoretical risk of harm if a unit which signals positive after issue contains slow-growing pathogenic bacteria, and has already been transfused. In practice, this has not been seen. However, such recalls lead to additional anxiety for the patient and involve assessment of the patient with possible need for antibiotics.

Component recall involves considerable additional work for the Blood Services and the hospitals, and the subsequent management of the donors involved.

Table 9 estimates the number of components that would require recall at different proportions of apheresis collection, using the following assumptions:

- Each initial reactive of an apheresis platelet will lead to 2.14 units being recalled
- Each initial reactive of a pooled platelet will lead to 4 units of red cells and one pooled platelet being recalled
- Initial reactive rates used as given in table 3
- Number of units produced per year = 272,100.

Table 9. Estimated component recalls at different % of platelets collected by apheresis

	Recalls per year			
% apheresis	**80%**	**50%**	**35%**	**20%**
Platelet units	2,530	1,959	1,673	1,388
Red cell units	805	2,013	2,617	3,222
Total units	3,335	3,972	4,290	4,610

If the SaBTO recommendation on apheresis platelets is accepted by the UK Blood Services, it is likely that at least some (certainly NHSBT) will begin to decrease the percentage of platelets produced from apheresis. With a decreasing percentage of apheresis, fewer platelet units will require recall from hospitals. However, through an associated increase in buffy coat platelets, an increasing number of red cell units will require recall, though because of the much longer shelf life, these are less likely to have been issued to hospitals. However, these units will be removed from stock and investigated, reducing the number of red cells available for transfusion.

Suspected bacterial transmissions

In 2012 there were 23 cases of suspected transfusion-transmitted bacterial infection reported to the NHSBT National Bacteriology Laboratory for investigation after transfusion of apheresis platelets, compared to 5 cases after transfusion of pooled platelets (none was confirmed positive). This reflects the current split of 80% of platelets being derived from apheresis.

Recent 'near-miss' incident: apheresis platelets contaminated with *Staphylococcus aureus*

In September 2013 NHSBT reported their first bacterial screening 'miss' since screening began, during which time over 600,000 units had been screened.

11/09/13 Donation date: two units donated by apheresis, no adverse events reported
13/09/13: Pack 1 and pack 2 sampled for bacterial screening, each sampled by a different member of staff. All standard procedures were followed
14/09/13 Pack 2 issued to hospital A
15/09/13 Pack 1 issued to hospital B
16/09/13 Hospital A reported seeing clumps in the pack, both units recalled
18/09/13 Both packs returned for culture, clumps no longer visible in pack 2 but forming in pack 1. Both packs Gram stained and Gram-positive cocci observed. Samples taken from each pack and incubated on the BacT/Alert system; signalled reactive after 3.8 hours of incubation. Bottles were subcultured and isolates confirmed as *Staphylococcus aureus.* Further analysis showed that the isolates from pack 1 and pack 2 were indistinguishable. Bottles from routine bacterial screening had already been discarded at the end of the platelet shelf life.

The donor reported no significant medical history. Swabs were taken from the venepuncture site pre- and post- 'Chloroprep' cleansing, hair line and nostrils. *S. aureus* was isolated from the donor's nostrils. These isolates were found to be indistinguishable from those isolated from the platelet packs using molecular tying.

This is the first confirmed bacterial screening 'miss' since testing began in 2011. There is no evidence that the packs were not sampled or the bottles placed incorrectly on the machine. The most likely reason for the failure of detection is a lack of organisms being present in the original sample either due to 1) no bacteria captured in the initial sample due to low bacterial numbers in the pack or 2) the microorganisms growing in clumps/as a biofilm and not spread evenly through the pack. The donor was shown to be a carrier of *S. aureus*.

Conclusions

1. Bacterial screening has proved highly effective in removing platelets contaminated with pathogenic bacteria from the blood supply. There have

been no proven transmissions and one ‘near-miss’ in over 600,000 units tested. However, it is well recognised that screening early in storage can never be 100% effective.

2. The model of continuous culture to outdate potentially adds an additional layer of protection, but is associated with the problems of recalls.

3. Visual inspection of platelets prior to transfusion, and appreciation of the small but ongoing risk, remain important steps in contributing to overall safety.

4. PATHOGEN INACTIVATION SYSTEMS AVAILABLE / IN USE AND THEIR REGULATORY STATUS

Summary of systems

Three systems are under consideration, key aspects of which are given in Table 10.

Table 10. Systems for pathogen inactivation of platelets

	System A	System B	System C
Treatment	150mM Amotosalen + 3-4 J/cm2 UVA	50mM Riboflavin + 6.2 J/cm2 UV	0.2 J/cm2 UVC
Mechanism of action	Irreversible cross-linking of nucleic acid	Oxidation of guanine residues	Formation of pyrimidine dimers
Time to treat	4 mins	8-10 mins	1 min
Remove chemicals	Yes (6-16hours)	No	None added
Storage medium	Plasma PAS (PASIII or SSP+)	Plasma PAS (SSP+)	PAS (SSP+)
Shelf life	5 days plasma 7 days PAS	5 days plasma 7 days PAS	5 days
Can treat with one kit	Single or double dose	Single or double dose	Single Dose
Platelet loss due to process	10%	<5%	<5%
Regulatory classification	Class III	Class IIb	Class IIa for bag Class IIb for device

Two of the systems (A and B) are based on the addition of a photosensitising chemical to platelets followed by exposure to UV light. System C is based on the exposure of platelets to UVC light only, without the addition of any exogenous chemicals. All three result in blockage to nucleic acid replication, which in turn is necessary for pathogen replication, but not for platelets to function. The exact mechanism of action differs between the three systems. In system A, Amotosalen binds non-specifically to nucleic acid and when exposed to UVA light forms a permanent cross-link between nucleic acid strands. The microbiocidal effect of system C is mainly attributable to direct interaction with nucleic acids and the resulting formation of cyclobutane

pyrimidine and pyrimidine pyrimidone dimers that block the elongation of nucleic acid transcripts. In system B, riboflavin in conjunction with UV light associates with nucleic acids and mediates an oxygen-independent electron transfer process leading to the oxidation of guanine residues and strand breaks. For systems A and B, studies in rodent models have not revealed any evidence of genotoxicity.

The time taken to treat platelets is determined by the amount of energy required to be delivered to the platelet concentrate, but is in the order of a few minutes. In system A there is a step at the end of the treatment process that removes approximately 99% of the photosensitising chemical, a process that takes 6-16 hours. There is no removal step for system B, and the photosensitising chemical and its photodegredation products remain in the platelet bag.

All three systems are CE marked for a shelf life of 5 days, but this is extended to 7 days for systems A and B if platelets are stored in PAS (Intersol or SSP+).

For systems A and B, platelets can be treated as a single adult therapeutic dose (ATD), but a more cost-effective option is to treat two ATDs using a kit designed for that purpose. This is currently possible for apheresis platelets collected as a double ATD and also for buffy coat platelet concentrates by pooling 7 or more buffy coats to make a double ATD. The latter is in routine use for some centres in Europe for system A but not yet for system B. In system C platelets must be treated as a single dose.

Unless specifically adjusted for when PI systems are implemented (eg by adding an extra buffy coat for example), system A results in a reduction in platelet dose of approximately 10%, with less of a reduction for systems B or C (typically less than 5%) due to the reduced number of processing steps involved. Current methods for testing for bacterial contamination of platelets also reduce the dose of platelets by 10%, due to sampling of the product.

Regulatory issues

Pathogen inactivation systems are regarded in regulatory terms as medical devices and are CE marked as an indicator of conformance to EU legislation. EU directives determine the requirements that they must meet in order to be CE marked.

Medical devices are categorised according to the Medical Devices Directive (93/42/EEC) as either class I (low risk), class IIa or IIb (medium risk) or class III (high risk). This classification is determined by a number of factors including how long the device will be in continuous use, whether the device is invasive or implantable, and whether the device contains a substance which in its own right is considered to be a medicinal substance and has action ancillary to that of the device.

To obtain a CE mark, manufacturers must verify that that the product complies with essential criteria laid out in the relevant EU directives, and if the directive stipulates so, to have this examined by a notified body. A notified body is an impartial third party, designated by the Competent Authority (MHRA) as capable (having expert knowledge) and resourced to assess applications to specific Medical Device Directives. In general terms, pathogen inactivation systems for platelets under the current 'rules' would be regarded as class IIb devices. For class III devices, the notified body would be expected to review clinical data relating to the device, but this is not necessarily the case for class II devices.

System A has been CE marked as a class III medical device whereas system B is a Class IIb device. System C is CE marked as class IIa for the platelet bag and IIb for the illuminator. This difference in regulatory class influences the level of data required for CE marking, which is reflected in the amount of clinical data available. It is not clear why System A has been considered as class III whereas system B has not. This may relate to how the photosensitising chemicals were viewed by the notified body in terms of potential toxicological impact.

None of the systems has been approved by the US Food and Drug Administration (FDA). System A is undergoing a pre-marketing authorisation to the FDA for treatment of both plasma and platelet components. This is the process by which data is reviewed/approved for class III devices in the USA. Should that be successful, approval would not be expected before 2015, following review of clinical data. The application is for a 5 day shelf life in line with the market requirements in the USA.

The claims made by the manufacturers are summarised in Table 11. A detailed summary of the pathogen reduction claims is given in Table 11 below.

Although system C has obtained CE marking, the manufacturers are not marketing this product for sale until further clinical studies have been completed, since they believe that customer confidence is likely to be increased by such data.

NHSBT is currently clarifying with the MHRA whether PI would be regarded as a change to the existing blood establishment licence (to add a new component), or whether pathogen inactivated platelets would be viewed as a medicinal product.

Table 11. Claims made by manufacturers as part of CE mark or labelling

	System A	System B	System C
Pathogen reduction	Broad spectrum	Broad spectrum	Broad spectrum
Shelf life	Up to 7 days (in PAS) Up to 5 days in plasma	Up to 7 days (in PAS) Up to 5 days in plasma	Up to 5 days
Patient populations	No exclusions*	No exclusions	Not stated
Inactivation of leucocytes	Can replace gamma or x-irradiation	Can replace gamma or x-irradiation	Can replace gamma or x-irradiation
Inactivation of CMV	Can replace CMV seronegative serology	Can replace CMV seronegative serology	Not stated

*labelling states that treated units are not clinically different to conventional components

Operational considerations

Shelf life

The current maximum shelf life of platelets in the UK is 7 days, which was extended from 5 days following the introduction of bacterial screening. The 'usable' shelf life of components is determined by how soon after production they can be released for issue, and the maximal shelf life of the platelet. Currently platelets are held for sampling, and then until the initial bacterial screening results are available, the time for which varies depending upon the protocol for bacterial screening, which is not standardised across the four UK Blood Services. Currently in NHSBT platelets are available for issue on day 2/3 of storage. If pathogen inactivation were to replace bacterial screening, then platelets could be available to issue on day 1/2.

From an operational perspective, it is highly desirable to have as long a usable shelf life as possible to simplify stock management and reduce platelet wastage. The introduction of PI with a 7 day shelf life would potentially increase the useable shelf life of platelets by 1 day, and reduce the average age of platelets issued by at least 1 day.

Irradiation and cytomegalovirus testing

PI has the potential to obviate the need for irradiation of platelets to prevent transfusion-associated graft-versus-host disease (TA-GvHD), or the need to provide CMV seronegative components to prevent transmission of CMV due to its inactivation profile for leucocytes and viruses. In NHSBT approximately 50% of platelets are irradiated, and in SNBTS all platelets are irradiated. In 2012, SABTO recommended that leucocyte depleted components be used as

an alternative to CMV seronegative components for all recipients except pregnant women, neonates and intra-uterine transfusions. The implementation of this recommendation by hospitals has been variable to date, with some continuing to order CMV negative components. Although there would be a cost saving associated with stopping the requirement to irradiate or provide CMV seronegative components, this cannot be fully realised by platelet PI alone, as a requirement to irradiate and CMV test a proportion of red cells and granulocytes will remain. Nonetheless, the removal of these requirements would simplify platelet stock management within blood centres and hospitals.

Ability to meet specifications for platelets pre-treatment

The manufacturers of PI systems provide a set of specifications that platelet concentrate must meet prior to treatment (see Table 7).

Operational assessments of system A are currently being performed by NHSBT and SNBTS. Prior to implementation of any new process for blood component production, operational validations are undertaken by UK Blood Services to ensure that the product will meet set specifications and is efficacious and safe. These are in addition to the studies that will have been conducted by manufacturers as part of the CE marking process. The studies conducted by the UK Blood Services are divided into three stages: phase 0 studies are small scale laboratory studies designed to provide assurance that the component is effective and safe - Blood Services may also accept data from manufacturers rather than performing these studies themselves. Following satisfactory completion of phase 0, Operational Qualification (OQ) and Process Qualification (PQ) are performed on a larger number of units. OQ and PQ are designed to gain sufficient data to allow quality monitoring criteria to be set and to gain operational data on the system when it is used in routine practice.

The purpose of the OQ/PQ studies planned by NHSBT and SNBTS on PI platelets is primarily to gain an understanding of what resources will be required to produce platelets that meet the pre-treatment specifications laid down by the manufacturers and to assess the usable shelf life of the component in an operational setting.

Therefore at this stage there are limited data on the impact on UK Blood Services of implementing PI. It is likely that some optimisation of process will be required to ensure platelets meet the pre-defined specifications for treating them with PI systems. In particular, there are limited data available with respect to the feasibility of producing an adequate dose of platelets by pooling and treating a double dose of buffy coat-derived platelets.

Handling of the final product

In system B, there is a requirement to protect the final product from exposure to ambient light, since the photosensitising chemical used remains in the platelet bag during storage and can potentially lead to further interaction with

platelets when exposed to the UV wavelengths in normal daylight. Studies conducted by the manufacturer confirm that this is indeed the case and can impact on the quality of the component. In our opinion, the limits of exposure have been poorly defined and therefore there may be significant implications for blood centres and hospitals in being able to store these platelets appropriately so that their clinical effectiveness is not adversely affected. This requires further data to inform how these platelets should be handled following treatment, and it is not recommended to proceed to operational studies until this issue is better understood.

Plasma pathogen inactivation

It would be advantageous if any PI system for platelets was also capable of treating plasma components should NHSBT continue to produce single unit pathogen inactivated plasma. Both systems A and B can be used for this purpose and are under assessment by NHSBT.

Use of pathogen inactivation of platelets internationally

There is widespread use of both systems A and B in Europe as well as the Middle East (see Appendix 2). Most routine use of PI systems is within individual blood centres rather than through universal adoption of PI by National Blood Services. Therefore the universal implementation of system A to treat 100% of platelets in Switzerland is of particular note, as well as more than 90% of platelets treated in Belgium.

Although legally in most EU member states the shelf life of PI platelets is 7 days, many centres who have implemented PI of platelets have chosen a 5 day shelf life. Notably, Germany and France have not approved PI platelets beyond 5 days of storage.

System A

System A is in use in over 18 countries. To date over 1.1 million units of platelet concentrate have been transfused, with 350,000 units per year being treated globally. All Centres that routinely use system A treat and store platelets in PAS (either Intersol or SSP+), the majority only to 5 days with some to 7 days.

System B

System B is in routine use in over 15 countries. To date more than 150,000 units of platelet concentrate have been transfused with approximately 50,000 per year being treated globally. The majority of centres treat and store platelets in plasma to 5 days, with only two centres in Spain storing to 7 days when treated in SSP+.
There is greater uptake of system A in routine use than system B. It is not known whether this reflects the system being available for a longer period of time, or greater user confidence in the system, or a combination of both.

Table 12. Specifications for platelet components prior to pathogen inactivation by the manufacturer

Manufacturer A	Small Volume Set	Large Volume Set		Dual Storage Set
Suspension medium	PAS	PAS	Plasma	PAS
Platelet count	2.5-6.0 x 10^{11}	2.5-7.0 x 10^{11}	2.5-7.0 x 10^{11}	2.5-8.0 x 10^{11}
Volume	255-325ml	300-420ml	255-390ml	300-420ml
Plasma	32-47%	32-47%	100%	32-47%
RBC	<4x10^6 per ml	<4x10^6 per ml	<4x10^6 per ml	<4x10^6 per ml
CAD time	4-16 hours	6-16 hours	16-24 hours	6-16 hours
Maximum storage period	7 days	7 days	5 days	7 days
Integrated storage containers	1	1	1	2

Manufacturer B	Incoming Product Specification – prior to addition of Riboflavin		
	Treatment in 100% Plasma	PPC treatment with storage in PAS	Treatment in PAS
Volume	170-360ml	90-360ml	250-450ml
Platelet concentration	0.8-2.1x10^6/ul	1.75-3.4x10^6/ul	0.8-1.5x10^6/ul
Plasma	100%	100%	30-45%
Treatment yield	Not specified (up to 7.5x10^{11})	Not specified (up to 12.0x10^{11})	Not specified (up to 6.75x10^{11})
	Product Storage Specifications		
Volume/bag	170-400ml	250-400ml	150-435ml
Platelet concentration	0.7-2.1x10^6/ul	0.7-1.5x10^6/ul	0.7-1.5x10^6/ul
Yield per bag	<5.1x10^{11} (<4.5x10^{11} recommended for optimal 5 day storage)		

Manufacturer C	
Parameter	**Specification**
Volume	350ml (325-375ml)
Platelet concentration	0.8-1.2x10^9/ml
Plasma content	35 ± 5%
Ratio Plasma:SSP+	30:70 to 40:60

Status of pathogen inactivation for red cells / whole blood

Manufacturer A has a system which is being developed for pathogen inactivation of red blood cells, utilising the S-303 compound. When added to blood at neutral pH, the compound acts to irreversibly block the replication of DNA and RNA. Manufacturer A completed a Phase I clinical trial of this system in 2010. A Phase II trial is underway in the US and patient enrolment has been initiated in a European Phase III clinical trial in acute and chronic anaemia indications.

Manufacturer B is developing a system which uses Riboflavin and UV light. The system utilises the same processes as for PI of platelets. The process modifies the nucleic acid, irreversibly rendering pathogens unable to replicate. Manufacturer B has undertaken a Phase I clinical trial in the US. A Phase II trial is planned to be undertaken in the US and a second trial in Africa. An agreement has been reached between Manufacturer B and the US

Department of Defence to advance the system for the treatment of donated whole blood used in emergency transfusions in deployed military forces.

Conclusions

1. Platelet PI is being adopted to an extent in many countries, but only Switzerland has moved to 100% PI.

2. Systems are CE marked and can be adopted without further regulatory approvals. It remains unclear how adoption would affect Blood Services licences.

3. These systems could fit into Blood Service operations, but further operational evaluations are necessary.

4. Further work is needed to establish the post-treatment handling of platelets treated by system B with regard to protection from light.

5. PI would allow earlier release of platelets to stock than the current screening model used in NHSBT. It remains advantageous to permit a 7 day shelf life.

6. If manufacturers' claims regarding CMV and irradiation are accepted (see later sections), there would be considerable operational advantages for the end-to-end blood supply chain.

7. EFFICACY IN PATHOGEN INACTIVATION

Bacteria and parasites

The published peer-reviewed literature and claims provided by the manufacturers of the three PI systems under consideration (A, B and C) were reviewed to assess:

1. The efficiency and sensitivity of the assays to detect microorganisms that survived the process

2. The range and clinical validity of microorganisms tested for susceptibility to the inactivation process

3. The potential for failure of a PI system through regrowth of survivors

4. Additional studies required.

General considerations

Unlike viruses, bacteria can multiply during storage of a platelet product at 22°C and initially low numbers (around 100) of a fast growing organism can multiply to reach clinically relevant levels (10^6) in a relatively short time. The growth rates are influenced by the species, the initial inoculum, and oxygen and nutritional requirements. Some bacteria such as the facultative anaerobe *Propionibacterium acnes* may survive storage and maintain low numbers throughout the shelf life of a platelet product whereas Gram-negative species (*Klebsiella* and other gut coliforms), as well as *Staphylococcus aureus*, may grow to high numbers; these organisms are associated with a higher risk of morbidity and mortality compared with commensal skin and oral flora.

Determination of pathogen inactivation

The basic experimental design of bacterial inactivation studies, regardless of the system used, involve the spiking of a platelet unit of approximately 300 ml with a suspension of bacterial culture to give a concentration of approximately 10^5-10^6 per unit, which equates to 500 to 1,500 bacteria per ml. This level of contamination is believed to be greatly in excess of the numbers of bacteria that may be present in a unit as a result of contamination from a skin site or, less likely, asymptomatic bacteraemia in a donor. Following spiking, a sample of the unit is taken to determine the input titre and after the PI process, the post treatment titre is determined by culturing a representative sample volume and colony counting. Measurement of the log reduction of pathogen numbers is a valid tool for the evaluation of virus inactivation but the ability of bacteria to multiply during storage introduces areas of technical complexity due to clumping of bacterial cells, and sampling and counting errors.

The log reduction is expressed as the input titre/post treatment titre. For example, following an input titre of 10^6 bacteria if no growth is detected in 30 ml (10% of spiked unit volume) of the post treatment samples the titre would be calculated as < 0.03/ml or < 1.5 logs/ml giving a log reduction of approximately 5 logs. It should be noted that the post treatment volume assayed for some bacteria in published studies may be only 1% of the unit volume which is 10-fold below the European Pharmacopeia specification for sterility testing of a therapeutic product.

An alternative approach used in some experimental studies is to perform testing of a spiked product at intervals over the storage period of the platelet unit. This offers the advantage of detecting small numbers of bacteria which may have survived the inactivation process and thus have the potential to grow to clinically relevant numbers.

Comparison of log reduction data of pathogen inactivation systems

There are several published studies of the performance of Manufacturer A in challenge tests with platelet units spiked with high and low numbers of various microorganisms, and efficacy is expressed as numbers of log reduction. However, most of the data supporting efficacy of Manufacturer A stem from the foundation work of Lin et al.[7] and other Manufacturer A sponsored or collaborative studies (see Appendix 3). There are, however, fewer published data for Manufacturer B and Manufacturer C.

A summary of the organisms tested, the number of isolates used, and the log reductions obtained in the three systems is given in Table 13. Overall, higher rates of log reductions of several more bacterial species are claimed for Manufacturer A than for Manufacturer B or Manufacturer C. Of the 22 Gram-positive and Gram-negative species tested with Manufacturer A, 13 exhibited ≥ 6-logs reduction and only *Pseudomonas aeruginosa* and *Bacillus cereus* were less susceptible to the process. Post treatment titres of fewer species are reported for Manufacturer B but most ‘pathogens’ showed 3-4 logs reduction from the input titre, although this system was ineffective against *B. cereus*, *Acinetobacter* (a common skin colonist), and one of 5 strains of *S. aureus*. Fewer species were tested with Manufacturer C but generally reductions of viable counts of more than 4 logs were obtained.

Some bacteria grow better in PAS plus 35% plasma and exhibit reduced biofilm formation, which increases bacterial availability for sampling[8]. PAS initiated earlier log-phase growth of several species tested and resulted in a bacterial concentration 4 logs higher than found for plasma alone at 24 hours. This may present an earlier bacterial detection advantage for PAS-stored platelets [9]. An examination of a number of PAS formulations showed that

[7] Lin L et al. Photochemical treatment of platelet concentrates with amotosalen and long-wavelength ultraviolet light inactivates a broad spectrum of pathogenic bacteria. *Transfusion* 2004;**44**:1496-1504.
[8] Greco CA et al. *Transfusion* 2010;**50**:2344-2352
[9] Dumont LJ et al. *Transfusion* 2011;**51**:1079-1085

several are rich in glucose and compounds (acetate, citrate) which can be utilised by a range of species as nutrients for growth.

Suspension of platelets in PAS may provide a better platform for PI of some bacteria but the evidence is conflicting. In a comparative study, system B was more effective in eradicating some bacterial species (*S. epidermidis* and *Streptococcus pyogenes*) in PAS with 35% plasma than plasma alone while *K. pneumoniae* and *E. coli* were killed equally in either background[10]. Data for system A for four species (*K. pneumoniae*, *Y. enterocolitica*, *S. aureus* and *S. epidermidis*) show the reverse, as log reductions were generally 1-2 fold higher for the bacteria in plasma than in PAS. The data provided by the manufacturers for system B are for plasma alone and for 35% plasma in additive solution in system C.

Differences were reported between platelets in PAS compared with plasma alone. Where such comparisons were made with Manufacturer A, log reductions were generally 1-2 fold higher for the bacteria in plasma than PAS. Data for plasma only were presented for Manufacturer B and in 35% plasma for Manufacturer C.

Where tested, both Manufacturer A and Manufacturer B showed good activity against the spirochetes and Rickettsia, assayed by infectious doses in experimental animal models.

Correspondence of species tested with isolations from routine screening

A review of the bacteria isolated from platelets since the implementation of screening by NHSBT showed that of the 159 confirmed positive donations so far, 11 different 'significant' species were identified. Almost all of these species are well represented in the panels used by the manufacturers in log reduction tests, particularly for Manufacturer A and Manufacturer B (Table 1) but notable exceptions to this are *S. pneumoniae*, *S. bovis* and *Listeria monocytogenes* which were each isolated on three occasions from donations. Similarly, of the 14 species/groups implicated in the 35 incidents of transfusion-transmitted infections recorded from 1995 to 2009 (Table 5), only *S. pneumoniae* and *S. bovis* were not represented in the panels tested by the manufacturers. However, given the poor response of *B. cereus* to photoinactivation by all systems, it is of interest to note that this species was implicated in 5 of the above incidents, second only in frequency to *S. epidermidis*.

Potential for failure of a pathogen inactivation system

Although the log reduction data are on the whole indicative of good efficacy for killing of the great majority of potential pathogens, some experiments carried out by German workers but as yet presented only in poster format[11]

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[10] Stormer et al. 2010;99:Suppl 1:308

[11] Schmidt M et al. Efficiency of the pathogen inactivation system MANUFACTURER A® under experimental conditions. *Vox Sanguinis* 2011;**101**:Suppl 1.P-367

raise concern regarding the survival of two potentially highly pathogenic species following Manufacturer A inactivation, and their proliferation on storage. They contaminated both apheresis and pooled platelet units separately with 7 species in low (100 cfu/bag) and high (1000 cfu/bag) concentrations and following inactivation, samples were tested daily by BacT/ALERT for up to 7 days. Breakthrough was observed of one of the two *K. pneumoniae* strains tested at counts of 10^2 cfu/ml and 10^6 cfu/ml on days 4 and 5 respectively. Similar counts were found for *B. cereus* on the same days with units seeded with the highest inoculum (See Appendix 3). Interestingly, clear and reproducible evidence demonstrates that breakthrough of either organism was not found in experiments with apheresis platelets.

The survival of *B. cereus* was attributed to the probable presence of spores which are known to be impervious to photoinactivation, but this was not confirmed. This and other *Bacillus* species form spores as a survival mechanism against adverse environments and are highly resistant to chemical and physical agents. They revert to a vegetative state when heat-shocked or when favourable conditions return and then multiply rapidly. Stormer et al.[12] showed that colony counts of *B. cereus* spore suspensions introduced into a platelet unit at 5 cfu/ml proliferated over 7-day storage to almost 10^8/ml, but spores of *Clostridium sporogenes* did not enter vegetative phase under storage conditions.

The breakthrough of the *K. pneumoniae* strain is of particular concern as this organism and related bacteria historically account for most of the fatalities (82%) reported by SHOT 2002[13] for platelet incidents. Some specific serotypes of this species (approximately 5%) possess a dense polysaccharide capsule which is antiphagocytic and also impedes uptake of some compounds; no data are available on amotosalen uptake and UV penetration in such strains. Further testing of photoinactivation of a wider panel of strains of *K. pneumoniae* and other capsulated species (eg *S. pneumoniae* and *S. agalactiae*) are warranted to ensure that they are effectively killed by the systems.

Although there are demonstrable differences in the susceptibility of various species to UV light, there is no evidence that emergence of resistance occurs following exposure in a manner analogous to that seen with antibiotics.

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[12] Stormer M, et al. Spore-forming organisms in platelet concentrates: a challenge in transfusion bacterial safety. *Transfusion Medicine* 2008;**18**:371-376.

[13] SHOT 2002. Serious Hazards of Transfusion. Report 2000-2001.

Table 13. Summary of log reduction data of bacteria and parasites submitted for Manufacturer A (A), Manufacturer B (B) and Manufacturer C (C)

Microorganism	A (no.) [log_{10}]	B (no.) [log_{10}]	C (no.) [log_{10}]
Gram-positive species			
Staphylococcus aureus	(3) [6.6]	(5) [3.6- 4.8]	(1) [>4.7]
S. epidermidis	(7) [>6.6]	(4) [4.6]	(1) [4.8]
Streptococcus pyogenes	(1) [>6.8]	(1) [2.6]	-
Strep. agalactiae (GBS)	(1) [ND]	(1) [ND]	-
Strep. Mitis	-	(1) [3.7]	-
Enterococcus faecalis	(1) [ND]	-	-
Listeria monocytogenes	(1) [>6.3]	-	-
Corynebacterium	(1) [>6.3]	-	-
Bacillus cereus (spores)	(1) [3.6]	(1) [2.6]	(1) [4.3]*
B. cereus (vegetative)	(1) [>6.0]	(1) [2.0]	-
Bifidobacterium	(1) [>6.5]	-	-
Propionibacterium acnes	(1) [6.7]	(1) [100%]**	1 [4.5]
Lactobacillus	(1) [>6.9]	-	-
Clostridium perfringens (vegetative)	(1) [>7.0]	-	1 [4.7]
Gram-negative species			
Escherichia coli	(2) [>6.4]	(1) [4.4]	(1) [4.01]
Serratia marcescens	(2) [6.7]	(1) [4.0]	(1) [>4.9]
Klebsiella pneumoniae	(6) [>5.6]	(1) [100%]**	(1) [4.8]
Enterobacter cloacae	(1) [5.9]	(1) [100%]**	(1) [4.2]
Salmonella cholerasuis	(1) [>6.2]	-	-
Yersinia enterocolitica	(2) [>5.9]	(1) [100%]**	-
Pseudomonas aeruginosa	(2) [4.5]	(1) [>4.5]	(1) [>4.9]
Acinetobacter baumannii	-	(1) [1.8] (67%)	-
Spirochaetes			
Treponema pallidum (syphilis)	[>6.8]	-	-
Borrelia (Lyme)	[>6.8]	-	-
Rickettsia			
Orientia tsutsugamuchi (typhus)	[>5.0]	[>5.0]	-
Anaplasma	[>4.2]	-	-
Protozoa			
Plasmodium (malaria)	[>6.0]	[>3.2]	[4-5]
Trypanosoma cruzi (Chagas)	[>5.3]	[5.0]	[2.8-4.2]
Leishmania (promastigote)	[>5.0]	[>4.0]*	[>1.4]*
Leishmania (amastigote)	[>4.3]	?	?
Babesia	[>5.3]	[>4.0]	[>5]

* Spore forming and vegetative forms of *B. cereus* not differentiated; promastigotes and amastigotes of *Leishmania* not differentiated

** Percentage effective kill, log reduction not stated

Work in planning

Overall, the claims of the manufacturers regarding efficacy against most bacterial pathogens associated with contaminated platelets appear to be substantiated by the data available. However, there is a lack of independent and comparative studies on which to base decisions on the most effective system for routine use. For example, all but one of the published studies with Manufacturer A involve members of the manufacturers' corporation and this applies to a lesser degree to Manufacturer B and Manufacturer C. If these systems are intended to replace routine bacterial screening, independent studies addressing their capacity to inactivate completely low and high input inocula of multiple strains of 'high-risk' species (identified by bacterial screening), over the shelf life of the product, would seem prudent at this stage to increase assurance of efficacy. Also, it would be valuable to incorporate an element of destructive testing where more than 50% of the volume of spiked and treated units is sampled on expiry to ensure the absence of survivors. These studies could be completed in a relatively short time frame (3 months) if resources and platelet units were made available. This work has now been agreed within NHSBT.

Haemovigilance

Any good surveillance system is dependent on a robust reporting system, which in the case of TTI surveillance requires clinicians to be encouraged to report suspected TTIs which then can be further investigated, and a decision as to their imputability made. Imputability refers to the probability that a suspected TTI has been acquired by transfusion rather than another source. Suspected TTIs are usually reported as not proven, possible, probable or confirmed - the latter category requiring bacterial/viral identification in both the donor and recipient, usually with additional molecular typing to show that strains are indistinguishable.

International haemovigilance

There is an international haemovigilance network which contains countries from across Europe and the rest of the world. The haemovigilance systems vary between these countries, with many being based on the UK SHOT reporting system. A number of these countries publish annual haemovigilance data including data on the number of TTIs. In addition, within Europe data is collected by the European Directorate for the Quality of Medicines and HealthCare (EDQM) on viral markers in blood donors and TTIs and reported as an annual report[14]. Given the time taken to collect and analyse this information, the published information is always slightly out of date. The most recent report publically available is that from 2008[15]. EDQM

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[14] EDQM website

[15] EDQM Data 2008

also carry out additional surveys, including most recently a survey of the implementation of pathogen reduction technologies[16] (See Appendix 2).

Table 14. Countries with and without pathogen inactivation in use

Country	Pathogen Inactivation	Bacterial TTIs		
	2013	2009	2010	2011
Belgium	80%	No data freely available. Data from EDQM report suggestive of 6 in 2011		
Denmark	5-10%	1	1	0
France*	No PI	9 (241,634)	2 (253,149)	4 (267,785)
France PI	5-10%	0 (21,767)	0 (22,632)	0 (22,392)
Norway	5-10%	0	1	0
Spain	50%	2	0	1 (no comment about PI)
Sweden	20%	2	2	5
Switzerland	Not PI		1 (29,900)	0 (6,613)
Switzerland	PI			0 (26,454)
UK	Not PI	1	0	0

(number processed)
Source of data Cerus 2013. *French data for 2009 (most recent data available) does not correlate. Annual report 7 proven TTIs cf 9 TTIs.

Limitations of available surveillance data on breakthrough transmissions

- Most comparable surveillance data currently available pre-dates the implementation of pathogen reduction technologies in selected European countries.
- Not all countries have national haemovigilance systems in place; some collect regional data, or are in the early stages of implementation.
- There is little surveillance data available from countries where PI has been implemented.
- In countries with good surveillance the number of platelet doses treated by PI are relatively small and not sufficiently large to allow any comment to be made about the number of TTIs pre- and post-PI implementation.
- The only country which has implemented PI, has a good surveillance programme and relatively large numbers of processed platelets is France. However numbers treated to date are relatively small and surveillance data provided by Cerus do not correlate with that published by ANSM.

[16] EDQM PI Data

Sources of surveillance data

- Denmark DART
  http://www.haemovigilance.dk/pdf/DART_2011.pdf

- France
  http://ansm.sante.fr/var/ansm_site/storage/original/application/bb2a6b52bdb935954bd985d638e0e734.pdf

- Norway
  TROLL Paper Steinsvag CT, Espinosa A, Flesland O, Transfusion and Apheresis Science Eight years with haemovigilance in Norway. What have we learnt ? 2013
  http://www.sciencedirect.com/science/article/pii/S1473050213002966

- Spain
  http://www.msssi.gob.es/profesionales/saludPublica/medicinaTransfusional/hemovigilancia/docs/Informe2011.pdf

- Sweden
  http://www.transfusion.se/wp-content/uploads/2013/04/Hemovigilans-i-Sverige-2009-2011.pdf

- Switzerland
  http://www.swissmedic.ch/marktueberwachung/00159/00160/00437/index.html?lang=en;

Conclusions

1. Systems have broadly demonstrated adequate bacterial kill across the range of bacteria relevant to recipients of platelet transfusion. However, there is the potential for breakthrough transmissions, due to bacterial strains which are poorly penetrated by the chemicals, by spore formers, or by regrowth after treatment. Further work is planned to examine this potential.

2. It cannot be calculated whether PI is more or less effective than screening; both are likely to have efficacy close to, but not reaching, 100%. If PI were adopted, screening for bacteria could cease.

Viruses and other emerging infections

General considerations

Viral validation studies which are intended to assess the degree to which virus infectivity is eliminated or reduced are largely able to produce only approximate results. Model viruses and conditions employed in the studies may differ from those present in blood, and dose-related risk of transmission has not been defined for all pathogens tested; expression of log reduction is the accepted means to demonstrate efficacy; comparisons across different methodologies should be made with caution and with knowledge of the methods employed as they may differ substantially.

The highest titre of virus that can reasonably be employed should be added (spiked) into the product to be tested at a ratio not exceeding one part virus to nine parts sample. Although worst case conditions must be studied, this is limited by the fact that high titre virus stocks may be difficult or impossible to obtain, particularly for those viruses that cannot be grown in vitro.

Similar to tests for other pathogens, viral infectivity tests suffer from the limitation that the ability to detect low(er) viral concentrations depends on the size of the sample and the dynamic range and lower level of sensitivity of the methodology used.

For viruses, effectiveness of PI technology has been measured in a variety of ways, more frequently as TCID50, plaque reduction; occasionally, animal infectivity models and genome equivalents per ml have also been used.

Currently, viral inactivation and removal are part of an integrated process designed to guarantee the safety of some blood components; they have not yet replaced other safety measures such as screening of donations. PI technology for platelets adds another layer of safety but as far as virological risks are concerned, further comprehensive analysis will have to be made to the assess risks and benefits of changes to the other existing measures in order to maintain or improve the safety of our blood supply.

In terms of emerging arthropod-borne pathogens, such as West Nile Virus (WNV), it is perhaps worth noting the comment from the College of American Pathologists (WNV causes infection and clinical cases in America every year), that “infectious agents in blood product transfusions, such as .... West Nile virus, pale in comparison with bacterial contamination of platelets.”[17] Having said that, in August 2013 the Centers for Disease Control and Prevention (CDC) did report a fatal case of WNV disease after probable transfusion-associated transmission via platelets collected from an asymptomatic infected blood donor. In this case the donor was reactive when tested by WNV nucleic

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[17] Getting serious about platelet contamination. CAP Today. December 2002, Anne Paxton.

acid testing in a pool of donors, but non-reactive when each of the individual donors was tested[18]. Under EU legislation, either donor deferral or testing for WNV is required in travellers returning from WNV-endemic areas. PI could, in theory, substitute for either.

Viruses tested for, viral burden and screening methods

As a minimum requirement[19] [20] [21], viruses to be studied ought to include the classical transfusion-transmitted viruses and representative RNA and DNA viruses, both enveloped and non-enveloped, covering a wide range of physico-chemical properties amongst clinically relevant agents. Examples:

- Human Immunodeficiency Virus (HIV) type 1 and 2
- Hepatitis C Virus (a model for HCV such as Sindbis virus or Bovine viral diarrhoea virus)
- Hepatitis B Virus (HBV model - an enveloped DNA virus such as Pseudorabies virus or Duck HBV)
- Small, non-enveloped viruses such as hepatitis A virus, encephalomyocarditis virus (EMCV), or porcine parvovirus
- Large, enveloped RNA virus (Influenza)
- Large, enveloped DNA virus (CMV, herpes simplex virus).

The virus spike should be added to the product in a small volume so as to not dilute or alter the characteristics of the product. Typically, a spike of 5–10% of the total volume is employed. It is believed (but has not been individually verified) that manufacturers have complied with such requirements.

Inocula containing sufficiently high titres of viruses to reflect orders of magnitude encountered in vivo have not been used in all experiments due to technical difficulties in obtaining such material. Log reduction values must be interpreted with caution, in the context of methodology used and expected infectious load encountered in vivo.

Criteria employed

It is worth noting that the term pathogen inactivation needs to prove sterility of the product. Therefore it is also worth making the comparison below to illustrate the difference between bacteria and viruses. For bacteria, a sterile product is conventionally defined as one having less than one infectious organism in one million doses. No comparable figure has been agreed upon

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[18] CDC. MMWR Morb Mortal Wkly Rep 2013; 62(31):622-624 [summ., edited]
[19] WHO technical report, series no 924, 2004; annex 4 Guidelines on Viral Inactivation and removal procedures intended to assure the viral safety of human blood plasma products
[20] ICH Guideline on Viral Safety - Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin (Q5A*);* version 4, 1999.
[21] Guidance on Virus validation studies; the design, contribution and interpretation of studies validating the inactivation and removal of viruses. The European Agency for the evaluation of Medicinal Products. 1996

for viral sterility because viruses are more difficult to assay in the final product, the titre of virus in the stocks used to spike product is limited, and assessing the ability of a process to remove or inactivate viruses may suffer from significant variation.

A robust and effective process will be able to inactivate substantial amounts of virus, typically 4 logs or more; be easy to model convincingly, and be relatively insensitive to changes in process conditions.

Log reduction is often presented as > or ≥, either because of the limit of detection of the assay used or because there is no recoverable virus in the treated product, when a hypothetical value of 1 recoverable organism is used for the calculations.

Limitations and potential for failure of pathogen inactivation technology

Residual viable virus

The magnitude of expressed log reduction may be limited by the sensitivity and dynamic range of the systems used to measure the effect of treatment. On occasion (depending on the study design and limitations), complete log kill maybe achieved in vitro, but in the absence of a robust system that can test for inactivation of critical amounts of viruses, it is not possible to ascertain if viable pathogen would still be present in a real life situation; and if so, what the minimum infectious dose would have to be to result in transmission.
In some acute or chronic virus infection, it is not uncommon to see viral loads in excess of 10 orders of magnitude; in such situations, a demonstrable pathogen load reduction of 6 logs, for instance, would still leave significant amounts of infectious virus leading to infection in the recipient(s).

Variation in susceptibility and resistance to treatment

Non-enveloped viruses are challenging to inactivate because of the highly structured icosahedral nucleocapsid that has evolved to maintain viral integrity in hostile environments. This renders the penetration of certain molecules very difficult. Viruses belonging to the Picornaviridae family are classically used for verification of effectiveness of disinfection procedures due to their physico-chemical characteristics and resistance to treatment.

The susceptibility of non-enveloped viruses to PI technology varies significantly between different viruses, and to some extent between the different technologies available. Good efficacy can be seen with adenovirus and bluetongue virus, intermediate with parvovirus B19 and low with Picornaviruses. HAV and Poliovirus are resistant and HEV shows different degrees of susceptibility depending on the treatment type (see table 15).

It is of interest that the Japanese Red Cross has generated data demonstrating that one of the PI systems can efficiently inactivate live HEV in platelet concentrate, and so could be used to lower the possibility of HEV transmission through blood products. However, the limited infectious load of

HEV obtained from in vitro cultivation precluded an evaluation of reduction of infectivity beyond 3 orders of magnitude[22].

Emerging and re-emerging pathogens – the principle of precautionary measure

With regard to microbiological risks, the main argument for implementation of PI is the principle of precaution: protection against the unknown, new or re-emerging infectious agent. In recent years, several pathogens have been added to the list of potentially threatening agents which may carry transfusion-associated risks. These include Dengue virus, WNV, Chikungunya virus, Influenza A (H5N1), HIV and HBV variants and Babesia spp[23].

Chikungunya virus is a mosquito-borne alphavirus that recently re-emerged in Africa and rapidly spread into countries of the Indian Ocean basin and South-East Asia. The mean viraemic blood donation risk for Chikungunya virus on La Réunion reached 1.5% at the height of the 2005–2006 outbreaks. PI was successfully implemented at the time, following a demonstration of significant pathogen log reduction in plasma and platelets[24]. PI has also been used in Guadeloupe and Martinique during Dengue outbreaks and to minimise the risk of transfusion-associated transmission of T cruzi[25].

There is no doubt that there will be benefits from theoretical protection against threats whilst they are still unknown, and given the broad range of enveloped viruses that PI seems to have an effect on, this is an accepted advantage offered by the technology. Amongst viruses, the notable exception is the non-enveloped viruses, as already discussed. Another point of note is that should pathogen variants emerge, that would escape detection by established screening tests (eg WNV and HIV), the efficacy of PI would not be adversely affected.

The question of suitability of PI to deal with any potential future threat to the blood supply is a complex one and it cannot be analysed purely on the basis of efficacy of the technology against known pathogens.

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[22] Owada T, KanekoT, Matsumoto C, Igarashi M, Uchida S, SatakeM, Tadokoro M. Photochemical Inactivation of Hepatitis E Virus (HEV) in Platelet Samples (PCs) using Mirasol Pathogen Reduction Technology (PRT) System. AABB

[23] Stramer SL, Dodd RY, Subgroup AT-TDEID. Transfusion-transmitted emerging infectious diseases: 30 years of challenges and progress. Transfusion. 2013;53(10pt2):2375-83.

[24] Tsetsarkin KA, Sampson-Johannes A, Sawyer L, Kinsey J, Higgs S, Vanlandingham DL. Photochemical inactivation of Chikungunya virus in human apheresis platelet components by amotosalen and UVA light. American Journal of Tropical Medicine and Hygiene. 2013;88(6):1163-9.

[25] Kientz D, Waller C, Mendel I, Laforet M, Isola H, Cazenave JP. The frequency of transfusion related sepsis imputed to platelets – Impact of Pathogen inactivation . Abstract presented at 13th International Haemovigilance Seminar (IHS), Netherlands, Feb 2011

Vector-borne and zoonotic infections are likely to remain the most probable candidates for emergence and re-emergence[26], but local epidemiology may determine varying degrees of risk and potential to harm. Recognition of new pathogens, particularly viruses, and advances in the understanding of the pathogenesis of diseases will continue to contribute to additions to the list of transfusion-associated infections. There will be a need to evaluate and validate the robustness of PI to deal with such pathogens as they emerge. The next section explores one aspect of the laboratory requirements to meet this need.

Gaps in knowledge and suggestions for future work

The extent of documented inactivation of pathogens for which in vitro systems exist has been limited by the ability to generate sufficiently high-titre stocks for inoculation and the sensitivity of cell culture-based detection systems. Inactivation of a maximum of 4 to 6 log reduction in infectivity has been demonstrable if reduction has reached the lower limit of detection in the system employed. In light of viral loads during acute and in some cases chronic stages of infection that exceed these documented levels, there remains concern that PR alone is insufficient to fully safeguard the blood supply.

Although the technology can render some blood components safer, the level of acceptable risk varies under different circumstances and this must be fully considered. With implementation of active surveillance, accumulation of experience, and development of more robust systems to measure efficacy of log kill, evidence may be collected that will better inform assessment. Future availability of PI for red and white blood cells in the future will change the scenario significantly. Passive haemovigilance alone is not an acceptable risk indicator on which to base large scale implementation decisions. At the moment, donor testing will continue to be required for the agents currently screened for, and donor selection and deferral practices would need to be specifically risk assessed if PI for platelets were to be introduced.

Some significant human pathogens, such as HBV and HCV, do not have well characterised or adequately sensitive in vitro systems to study PI efficacy. Other agents that have presented difficulties for documentation of PI efficiency are parvovirus B19 and HEV. As new agents are discovered that present risks to the blood supply, there may be a significant lag in development of in vitro or animal model systems to evaluate PI efficacy. Additional approaches to evaluate pathogen inactivation procedures that can differentiate between damaged and intact nucleic acid in all clinically relevant pathogens, independent of the need to establish in vitro systems, would therefore be highly desirable.

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[26] Stramer SL, Hollinger FB, Katz LM, Kleinman S, Metzel PS, Gregory KR, et al. Emerging infectious disease agents and their potential threat to transfusion safety. Transfusion. 2009;49:1S-29S.

Conclusions

1. PI technologies have demonstrated multiple log inactivation of a broad range of viral and non-viral pathogens and relevant model viruses. There is evidence of a good level of pathogen reduction against most known viruses of accepted current relevance in transfusion microbiology. This translates into increased blood safety.

2. Manufacturer claims include substitution for CMV screening. PI, coupled with leucodepletion, should provide a sufficiently high degree of assurance to clinicians that CMV antibody screening of platelets could cease.

3. The above extends to some other viruses of emerging importance in transfusion microbiology. The demonstrable log reduction is highly dependent on the virus physico-chemical properties, as penetration of the active agent is a prerequisite for inactivation.

4. PI is currently seen as an additional, new line of defence, though there is not yet sufficient evidence to allow universal cessation or modification of donor testing and donor deferral. A phased out approach system for donor deferral due to travel may be an option for the future after individual risk assessments.

Table 15: Log reduction values supplied by the manufacturers (enveloped viruses)

Virus	**Log reduction**			**Family**	**Genome**	**Envelope**
PRT	**I**	**M**	**T**			
ENVELOPED VIRUSES						
Hepatitis B Virus (HBV)	>4.5->5.5	4.0 log gEq/ml		Hepadnaviridae	dsDNA	Y
Duck hepatitis virus (model for human HBV)	4.4- >6.2					
HCV	>4.5	≥4.1	.5.0	Flaviviridae	ssRNA	Y
BVDV (model for Flaviviruses)	≥5.4->6.0		≥2.74			
Sindbis (model for Flaviviruses)			≥5.2		ssRNA	Y
Human Immunodefficiency Virus -1	>3.4 ->6.7	4.5 - 5.9	1	Retroviridae	ssRNA	Y
Human Tcell Lymphotropic Virus type 1	≥4.5 - 4.7	no data		Retroviridae	ssRNA	Y
Human Tcell Lymphotropic Virus type 2	>5.7->5.9					
Human Cytomegalovirus (hCMV)	>5.9			Herpesviridae	dsDNA	Y
Pseudorabies (model for CMV)	>4.7 - >5.1	2.8		Herpesviridae	dsDNA	Y
Murine Cytomegalovirus (mCMV)		transmission of 6logs cell-free or cell-associated virus prevented		Herpesviridae	dsDNA	Y
West Nile Virus (WNV)	>6.0 -≥6.8	≥5.1	3.5-4.0	Flaviviridae	ssRNA	Y
Dengue	>5.3			Flaviviridae	ssRNA	Y
Chikungunya virus	>6.4 - ≥7.6	2.2		Togaviridae	ssRNA	Y
La Crosse Virus (LCV)		≥3.3		Bunyaviridae	ssRNA	
Influenza A H2N1		>5	>5.0	Orthomyxoviridae	ssRNA	Y
Influenza A H5N1	>5.7 - >5.9					
SARS-associated Corona Virus	≥5.5 - >6.2			Coronaviridae	ssRNA	Y
Vesicular stomatitis virus (VSV)		>6.3	≥6.3	Rhabidoviridae	ssRNA	Y
Crimean Congo Hemorhagic Virus	>2.9			Bunyaviridae	ssRNA	Y

Where data was not supplied, the cell was left blank. One of the manufacturers supplied data of platelets suspended in PAS+35% plasma and 100% plasma, hence two values presented in the table as a range.

Table 16: Log reduction values supplied by the manufacturers (non-enveloped viruses)

Virus	Log reduction			Family	Genome	Envelope
PRT	**I**	**M**	**T**			
			NON-ENVELOPED VIRUSES			
Hepatitis A Virus (HAV)	<1.3	1.8		Picornaviridae	ssRNA	N
Encephalomyocarditis virus (ECV) (model for HAV)		3.2	4	Picornaviridae	ssRNA	N
Bluetongue virus (model for non-enveloped and double stranded RNA virus)	5.1- 6.3			Reoviridae	dsRNA	N
Hepatitis E Virus (HEV)				Hepeviridae	ssRNA	N
genotype 3		≥3.0				
genotype 4		≥2.0				
Feline Calicivirus (model for non-enveloped virus, HEV)	2.1			Caliciviridae	ssRNA	N
Human Adenovirus	>5.9 - >6.9			Adenoviridae	dsDNA	N
Human Parvovirus B19	1.8 - >6.0			Parvoviridae	ssDNA	N
Canine Parvovirus						N
Porcine Parvovirus (PPV)	0	≥5.0	5	Parvoviridae	ssDNA	N

Where data was not supplied, the cell was left blank. One of the manufacturers supplied data of platelets suspended in PAS+35% plasma and 100% plasma, hence two values presented in column I as a range.

8. CLINICAL SAFETY AND EFFICACY

Remit and Methods

The remit of the Clinical sub group was to address the clinical advantages and disadvantages of pathogen inactivated platelets (PI-p) compared to appropriate standard product (S-p). The group considered the evidence from laboratory functional assays of platelets; from platelet recovery and survival studies in healthy volunteers; for patients of different age groups (adult, 1-16 years, less than 1 year); and factors of possible benefit to donors.

Although the initial approach was to consider the overall PI process rather than individual technologies, it became evident that the individual technologies had to be considered in reviewing the clinical evidence.

The group noted that PAS was likely to introduced prior to/in association with PI.

In reviewing the evidence, the group identified study end points that have high clinical importance:

- Bleeding or surrogates of bleeding: surrogates being corrected count increment (CCI) at 1 hour or 24 hours after transfusion. CCI is the post-transfusion minus pre-transfusion platelet count divided by the number of administered platelets, multiplied by the patient's body surface area. (Count increment (CI) is post-transfusion minus pre-transfusion platelet count)
- Alloimmunisation and refractoriness (clinical, immunologic, based on CCI, CI. Most studies define the term refractory if 2 sequential hourly post-transfusion platelet increments are less than 11×10^9/L)
- Need for increased platelet doses
- Infection with known and unknown pathogens (to be dealt with by the Infection sub group).

There were, however, limitations in their interpretation. Whilst bleeding end points are critical, the platelet count is the criterion used to determine the need for prophylactic platelet transfusion. Most clinicians and guidelines use numeric cut-offs for platelet thresholds prior to interventions eg epidural in obstetric practice, intrathecal chemotherapy, operations on the central nervous system etc. Trials of PI hitherto have not been large enough to detect differences in bleeding end points but are consistent in detecting differences in CCI , CI at 1hour and importantly at 24 hours. Calculation of CCI requires the platelet count in the bag transfused, but this is not usually available outside the trials setting, so CI is commonly used in clinical practice. It is likely that clinical practice will continue to be based on numerical thresholds, especially in view of data from recent platelet trials in different groups of patients with malignant haematological disease. In this report CI and the more robust CCI will be assessed as clinically valid indicators in the absence of robust data on bleeding outcomes, although there is ongoing debate as to the clinical validity of these measures.

There was a lack of clarity from the source literature as to the characteristics of the S-p, and how the S-p relates to current UK platelet components. UK platelet components have recently undergone a volume reduction as a consequence of the introduction of bacterial screening, but the clinical impact of this reduction has not been assessed. Therefore, consideration had to be given to the similarity (or otherwise) of the S-p components cited in source literature to current UK platelet components, and the impact on UK component volume of additional volume loss with PI technology but volume gain with withdrawal of bacterial screening technology. End points were considered for both systems.

Sources that were examined included the Cochrane review and papers cited in the review; further papers arising from the Cochrane review; data from manufacturers; data submitted by NHSBT, and data submitted by the secretariat. For raw data, please refer to the Cochrane review.

Results for Patients

System A and System B were considered separately. We found no differences in the broad conclusions.

Adults

There was no difference in mortality, serious adverse events, transfusion reactions or transfusion-related acute lung injury (TRALI) between patients treated with PI-p and S-p.

There was no statistically significant difference in bleeding risk for 'significant bleeding' as calculated by established scoring systems. However there was a trend to a small increase in 'less severe bleeding'. There was no difference in the use of red cells in patients receiving PI-p. Two RCTs using both system A and System B are ongoing. The studies may be able to provide some clarity to these questions within the next two years but some of the limitations described above remain.
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Surrogates for bleeding

There is a statistically significant reduction in CCI and CI at 1 hour and 24 hours. CI at 1 hour and 24 hours was better in S-p compared to System A platelets; there are no CI data reported by the one study reporting on System B platelets.
CCI at 1 hour and 24 hours was better in S-p compared to System A and System B platelets. This difference did not achieve statistical significance for System B platelets at 24 hours. There was also no statistically significant difference in paediatric patients. Although there was some suggestion that these decreases were minimised if platelet bag volume and platelet dose per bag were optimised to compensate for PI-process related loss, this did not entirely account for worse counts in patients after PI-p transfusion. This raised the question of whether there were other issues such as reduction in in-vivo viability that caused lower increments in patients. The magnitude of this was not clear from published work.

Alloimmunisation

There was no increase or reduction in alloimmunisation reported although few studies addressed this systematically. No neoantigens were found with Manufacturer

A platelets. Refractoriness (as defined by more than 2 consecutive failures in CCI or CI) was increased and it was not possible to assess whether this was due to alloimmunisation and/or other factors. This may however simply reflect the definition of refractoriness in some studies as being a lower CI / CCI and did not imply clinical refractoriness. If time-to-next-transfusion is considered, S-p were better (ie longer transfusion intervals) compared to Manufacturer A platelets; on the basis of one study, there was no difference in Manufacturer B platelets.

Dose

There was a small increase in total requirements of platelets by patients, reaching statistical significance in some studies but not others. This seemed to be present despite an increased volume per bag to compensate for PI process related loss. It was not possible to say whether the increased need for platelets related to alloimmunisation or refractoriness. There was a 7-10% increase in the number of platelet transfusions per patient from the Cochrane data. This range needs to be interpreted carefully as the studies citing this are of heterogeneous quality. Platelet transfusion interval was reduced to a small extent.

Transfusion-associated graft-versus-host disease (TA-GvHD)

Although there was a lack of good clinical data, it was accepted that animal and in vitro data can serve as surrogates since (TA-GvHD) is rare and would require a robust haemovigilance system to be able to calculate the risk. These data are convincing and indicate that gamma irradiation is not required in addition to PI-p to prevent TA-GvHD. Several countries have ceased irradiation with the adoption of PI technology and there have been no untoward effects.

Children and neonates

Although data on children are limited, there are no suggestions that use of PI-p in this population is contra-indicated. However, post-implementation monitoring will be required in this group. Furthermore, neonatal patients who require platelet transfusion during phototherapy for treatment of hyperbilirubinaemia should be treated with phototherapy devices that do not emit light less than 425 nm, to avoid the theoretical potentiation of an interaction between UVA light and psoralen, which may result in erythema.

Donor

Most studies have increased volume of collection per apheresis donation or pooled more donor buffy coats to constitute a bag of pooled platelets in order to compensate for PI process related loss. This increase is in the range of 10% of the volume. In the UK this may be achieved by ceasing bacterial testing, and it is estimated that the volume saved in so doing will compensate for loss by PI procedure. Thus volume per donation would be expected to remain unchanged. These assumptions are based on extrapolated data; as mentioned above, there may be an in vivo effect on platelet function/survival as a consequence of the PI technology that is independent of a volume effect. Temporary donor deferral for platelet donors will reduce due to removal of the requirement to defer following an initial reactive result of bacterial screening. There is potential for removing some travel restrictions eg visiting WNV or malaria affected areas; however, if there is a shift from apheresis to pooled platelets

this will be less relevant as pathogen inactivation of red cells is not under consideration.

Product handling after treatment

Limited data from Manufacturer B treated platelets show that ambient light can affect the in vivo recovery of platelets; this deterioration is more marked after 4 hours of exposure to ambient light. Processing of samples from bags treated with Manufacturer B's system will also require to be protected from ambient light. Thus operational issues are significant with Manufacturer B treated platelets; clinical issues can be significant if proper procedure is not adhered to.

Shelf life

Storage data for PI-p show adequate recovery at 5 days. There are published data from controlled clinical studies that have assessed both CCI and bleeding for manufacturer A platelets to day 7. However such data for manufacturer B are lacking. Therefore extension of shelf life to 7 days for manufacturer B-treated platelets requires further assessment when data from ongoing controlled clinical studies are available. PAS as the suspension fluid for PI-platelets may carry an advantage of fewer reactions; however studies show neutral rather than improved outcome with respect to transfusion reactions. Residual microparticles and amatosalen are not significant.

Processing time is minimally increased, however due to the extended hold pre-bacterial screening, the platelet components will be available for issue 1 day sooner than currently and the 'usable' shelf life of each unit will be extended by 1 day if a 7 day shelf life is retained. Some centres have ceased leucodepletion with the adoption of PI-p but this is unlikely to be considered in UK. Product recall due to initial reactive results of bacterial screening will reduce significantly. This has implications for all components generated from a given donor episode and represents an important benefit of PI to Blood Services and users (hospitals).

Impact of reducing apheresis platelets from 80%

Pooled platelets suspended in PAS are likely to replace a proportion of apheresis platelets over time. This will enable easier adoption of PI technology.

Conclusions

1. The clinical sub group considered that there were important advantages with PI-p, but these should be recognised alongside other limitations.

2. Red cells and plasma are not being considered for PI, therefore the impact of PI on transfusion-transmitted infections (TTIs) remains difficult to quantitate resulting in TTI remaining a pertinent issue.

3. The lack of need for irradiation will be of benefit to the providers and hospitals. However, red cells may need to be irradiated, thus clinical and governance procedures at provider and user ends will need to be continued.

4. Fewer apheresis platelet donors will need to be deferred as per existing criteria; this will not impact on pooled platelet donors.

5. A significant reduction in product recalls might be expected and will be of benefit to the providers and to hospitals.

6. However, there are drawbacks with regard to the clinical efficacy of PI-p, as detailed above. As stated, within the remit and methodology, we placed a greater value on some clinical outcomes. In these, PI-p were worse than S-p. The magnitude of this is hard to ascertain as specific issues (eg alloimmunisation) were not subject to robust studies. We estimate that there is likely to be a 5% increase in the use of platelets due to these issues if PI-p were to be implemented.

7. The procedural implications of using manufacturer B products are also of concern as detailed in product handling. Furthermore there are few studies assessing manufacturer B platelets in comparison to standard platelets.

8. The lack of data on neonates and children raises the need for post-implementation haemovigilance in this group of recipients.

9. Use of PI-p in non-haematology situations may be considered by extrapolating data from haematology studies.

9. COST-EFFECTIVENESS[27]

Since SaBTO last considered PI, there have been a number of developments in the way that we anticipate that platelets will be produced. First, the UK Blood Services now use bacterial screening; and second, we anticipate that the proportion of platelets that are procured by apheresis will reduce, although we do not yet know to what level.

Introducing PI would further affect the production process. UK Blood Services would be able to remove bacterial screening (and the resulting confirmatory testing and unit recall) and irradiation. We also assume that the wastage rate would reduce by 0.75% as a result of units being available for issue more quickly where the shelf life remains at 7 days, but assume that the rate would increase by 1% where the shelf life is reduced to 5 days[28]. The Clinical sub group also suggested that the introduction of PI may lead to an increase in the demand for platelet units of up to 5%. For this analysis, we consider the two extremes of a 0% and a 5% increase. For the analysis, we have also assumed that introducing PI would not change the number of deaths resulting from haemorrhaging.

The introduction of PI would also have an impact on the likelihood of TTI. We have restricted our modelling to bacterial infection[29] and, if the demand does increase, to vCJD infection. We have used information on confirmed positives from bacterial screening to date to estimate the total prevalence of relevant bacteria, and then compared this with information from SHOT over the period 2003-2010 to estimate the likelihood of a transfusion resulting in treatment, and the likelihood of death. We estimate that the cost of treating a bacterial infection is around £9,200[30], and that preventing a death resulting from bacterial infection would save 9.1 life years.

We have assumed that bacterial screening will identify 74 out of 75 units infected with relevant bacteria (roughly equivalent to missing one relevant bacteria-infected unit per 500,000 platelet units issued). For the purpose of the analysis, we have also assumed that PI will render 74 out of 75 infected units clinically safe. However, with bacterial screening, we estimate that 41% of recalled units have already been issued, and that 64% of those issued have already been transfused.
To estimate the impact of extra vCJD infections resulting from extra units being transfused, we have used the results from the September 2013 paper to inform the decision regarding apheresis. By assuming that all future cases result from transfusions in the next 20 years, we can use these previous results to estimate the expected number of symptom-free life-years lost per extra unit of platelets

[27] This section provides an overview of the calculations and results of the cost-effectiveness analysis. A fuller presentation appears at Appendix 4.
[28] Manufacturer A's system has CE marking for 7 day use, backed up by clinical evidence; Manufacturer B's has CE marking for 7 day shelf life, but without clinical evidence, and so we consider both 5 and 7 day shelf life; Manufacturer C's has CE marking for 5 day shelf life.
[29] Here we consider all bacteria other than Gram positive rods-skin flora, which are considered unlikely to cause harm.
[30] This is calculated by uplifting an estimate of £5,400 data from a 1998 study into Healthcare Acquired Infections into 2012/13 terms using the Hospital and Community Health Services Pay & Prices index, and then into 2013/14 terms using the Consumer Prices Health Index.

transfused, and thus assess the expected number of extra cases resulting from the extra transfusions in a year.

The various costs will depend on the percentage of units that are procured by apheresis, and whether there is an increase in the demand for platelets. Table 18 shows the costs and life-year implications if we assume a 5% increase in the demand for platelets, and that 35% of units are procured by apheresis.

Table 18: Costs and costs per life-year saved for alternative pathogen inactivation systems assuming 35% apheresis and a 5% increase in demand resulting from pathogen inactivation

	Baseline	Manuf'r A	Manuf'r B (7 days)	Manuf'r B (5 days)	Manuf'r C
Production costs per year	£21.8m	£22.7m	£22.7m	£23.1m	£23.1m
Screening & irrad'n/PI costs per year	£3.8m	Range from £8.0m to £16.1m			
Total annual costs	£25.5m	Range from £30.7m to £39.2m			
Total cost of PI		Range from £5.1m to £13.6m			
Life-years lost - bacteria	2.5	0.1	0.1	0.1	0.1
Life-years lost - vCJD	21.9	23.0	23.0	23.0	23.0
Total life-years lost	24.4	23.1	23.1	23.1	23.1
Life-years saved by PI		1.3	1.3	1.3	1.3

Note: Clinical treatment costs are below £50,000 and so not shown in the table. More detail of this and other calculations is provided in Appendix 4.

SaBTO has adopted a "safety framework" to inform its decisions about the introduction or withdrawal of safety measures. Under this framework, we consider the cost-effectiveness of a measure for recipients aged 60 or under. A separate "equity cost relating to the provision for over-60s" is also calculated, where a value is attached to the life-years saved among these older patients and subtracted from the cost of implementing the measure for the patient group. We therefore need to identify the costs and life-years saved for the two groups separately.

We estimate that patients aged over 60 receive around 39% of platelets[31] that are transfused, and therefore account for the same proportion of the costs. We also assume that they will account for the same proportion of bacteria-related deaths[32] zand around 1.2% of projected clinical vCJD cases. We also estimate 3.8 life-years lost per bacteria-related death in this age-group.

[31] Wells AW, Llewelyn CA, Casbard A, *et al* (2009): The EASTR Study: indications for transfusion and estimates of transfusion recipient numbers in hospitals supplied by the National Blood Service. *Transfusion Medicine*, 2009, 19, 0-0. (data on transfusions to patients aged over 60 was provided by A. Wells)

[32] We note that this is likely to be an underestimate, resulting in more life-years remaining to the under-60s and a more favourable cost-effectiveness calculation.

Table 19 shows the resulting equity cost and cost-effectiveness calculations.

Table 19: Equity costs and costs per life-year saved for patients aged under 60 for alternative pathogen inactivation systems assuming 35% apheresis and a 5% increase in demand resulting from pathogen inactivation

	Baseline	Manuf'r A	Manuf'r B (7 days)	Manuf'r B (5 days)	Manuf'r C
Total cost of PI per year		Range from £5.1m to £13.6m			
% units over 60		39%	39%	39%	39%
Equity cost		Range from £2.0m to £5.3m			
Cost for under-60s per year		Range from £3.1m to £8.3m			
Life-years lost for under-60s per year	24.0	23.1	23.1	23.1	23.1
Life-years saved by PI per year		0.9	0.9	0.9	0.9
Cost/life-year		Range from £3.4m to £9.1m			

Repeating these calculations for the alternative scenarios with 50% and 20% apheresis, and with no extra demand for platelets, gives the following table for cost per life-year saved.

Table 20: Cost per life-year saved (£m/life-year) for the alternative pathogen inactivation systems, with alternative levels of apheresis and increase in demand

% units by apheresis	Increase in platelet demand	Manuf'r A	Manuf'r B (7 days)	Manuf'r B (5 days)	Manuf'r C
20%	0%	Range from £1.0m to £3.2m			
35%	0%	Range from £1.1m to £3.6m			
50%	0%	Range from £1.3m to £4.0m			
20%	5%	Range from £2.6m to £7.1m			
35%	5%	Range from £3.4m to £9.1m			
50%	5%	Range from £4.7m to £12.2m			

The table shows that the cost per life-year saved is at least £1 million for each option, under each scenario, which is significantly higher than the current threshold of around £25,000 per Quality-Adjusted Life-Year (QALY) saved which SaBTO use as a comparator for cost-effectiveness purposes.

The figures presented so far relate to the running costs that we have been able to estimate. They do not include the cost of the actual recall process; the benefit of not needing to have a separate product line for irradiated platelets; the hospitals' costs for handling the extra units if demand does increase; and the benefits from identifying donors' clinical conditions as a result of bacterial screening. The first two

of these will tend to improve the cost-effectiveness of PI while the last two will tend to reduce the cost-effectiveness.

The calculations also do not include the capital costs of PI. Manufacturer A says that between 10 and 12 illuminators would be needed, Manufacturer B that 15 illuminators would be needed, and Manufacturer C that 15 UV machines would be required. We also understand that the process for Manufacturer A would require incubators, although we do not know what investment this would require. We understand that there are no corresponding capital costs for the current bacterial screening process as the machines are hired.

10. OBSERVATIONS AND RECOMMENDATIONS

Working group observations and recommendations for UK Blood Services

1. Pathogen inactivation technologies for platelets would be suitable to replace bacterial screening, with advantages in allowing earlier issue, lack of recalls and improved stock management.

2. Specifically, pathogen inactivation of platelets using the system from Manufacturer A would potentially be a safe and effective alternative to bacterial screening.

3. Pathogen inactivation of platelets using the system from Manufacturer B is not currently recommended as an alternative to bacterial screening, pending further information from clinical trials to support a 7 day shelf life and on the post-treatment handling of platelets with regard to protection from ambient light.

4. Pathogen inactivation of platelets using the system from manufacturer C is not currently recommended as an alternative to bacterial screening, due to lack of evidence of clinical effectiveness. (The manufacturers are not marketing this product for sale until further clinical studies have been completed).

5. Further studies of certain bacterial strains should be performed now to gain clarity regarding the limitations of each pathogen inactivation system.

6. Pathogen inactivation technologies A and B provide additional assurance with regard to cytomegalovirus safety (in combination with leucocyte depletion), so if either were implemented, serology testing could cease.

7. It is premature to recommend that any pathogen inactivation system should replace any aspect of current screening for HIV, hepatitis C and hepatitis B.

8. Emerging viral infections, including West Nile Virus and hepatitis E, are likely to be eliminated by pathogen inactivation, but each must be considered individually against each system.

9. Pathogen inactivation technologies A and B can replace irradiation of platelets for the prevention of transfusion-associated graft-versus-host disease.

10. Operational planning should assume an increase in demand for platelets by 5%.

11. There are no clinical groups for whom pathogen inactivated platelets should be withheld, although neonates requiring phototherapy require special risk assessment.

12. Robust haemovigilance systems should be in place before implementation to detect rare complications, particularly for children and infants.

13. Although there are clinical and operational advantages of pathogen inactivation, all systems would add considerable cost to platelet provision at current prices. Operational evaluations and dialogue with manufacturers should continue, to establish how implementation costs could be reduced.

14. Taking account of the evidence presented within this review, UK Blood Services should develop a structure and criteria for evaluating and approving new/existing CE-marked systems to pathogen inactivate blood components. Such criteria will obviate the necessity for further review of specific systems by SaBTO.

Working group recommendation to SaBTO

The driver to recommend pathogen inactivation for platelets, in the absence of systems for red cells/whole blood, would be to provide enhanced safety with regard to bacterial transmission. Clear evidence of overall clinical benefit, however, is not apparent at this time:

- Current bacterial screening, combined with diversion pouches and enhanced skin cleansing, is already providing a high degree of bacterial safety, with no reported case of transfusion-transmitted infection in platelets since 2009
- The limitations of pathogen inactivation with regard to certain strains of pathogenic bacterial species remain to be clarified through further studies
- The estimated increase in demand will increase donor exposure and hence potential risks from complications not reduced by either pathogen inactivation or Platelet Additive Solution
- System benefits, such as removal of irradiation machines and travel deferrals, cannot accrue until there are pathogen inactivation systems suitable for either red cells or whole blood. Under the current circumstances, therefore, the cost-effectiveness of pathogen inactivation remains very low.

For these reasons, implementation of pathogen inactivation of platelets is not currently recommended for the UK Blood Services. The issue should be reviewed again if significant new information becomes available with respect to the issues mentioned above, and/or if costs compared to bacterial screening are significantly reduced.

11. APPENDICES

Appendix 1

Pathogen Inactivation of Platelets Working Group

The Remit and Terms of Reference

Background

1. Bacterial contamination of platelet components is a recognised serious, potentially life-threatening, hazard of transfusion. It is the commonest transfusion-transmitted infection. Since 1996, there have been 34 confirmed cases of bacterial transmission from platelets reported to the Serious Hazards of Transfusion (SHOT) haemovigilance scheme, resulting in 8 deaths. In 2011 NHSBT commenced bacterial screening of all platelet components as a preventative measure. The bacterial screening has been an effective measure resulting in a significant reduction of clinical bacterial transmission. There have been no confirmed cases since 2010. However bacterial screening does not provide 100% efficacy in preventing bacterial transmission and results in the requirement from product recall. NHSBT contracts for equipment for bacterial testing of platelets are due for renewal in 2014.
2. Pathogen inactivation could be used to reduce the risk of bacterial contamination of platelets and has other benefits including the potential decreased risk from emerging infections.
3. The Advisory Committee on the Safety of Blood, Tissues and Organs (SaBTO) has previously considered technologies for pathogen inactivation of platelets in 2009 and 2010. In 2010, the working group reported that, cost effectiveness calculations demonstrated that after considering the potential benefits, and taking into account potential underreporting of transfusion-transmitted infection, pathogen inactivation would not be cost effective.
   At the time limited data was available related to the efficacy and safety of pathogen reduced platelets. A trial using pathogen reduced platelets undertaken in the Netherlands in 2009 (HOVON 82) was terminated due to an increase in bleeding episodes and differences in platelet count increment.
   Given the reported lack of cost effectiveness and significant concerns over the safety of pathogen reduced platelets SaBTO determined that introduction of pathogen inactivation technologies was not recommended
4. Since the 2010 review further clinical data have become available on pathogen inactivation of platelets. There have been two meta-analyses (including a systematic review) of clinical studies on pathogen inactivation platelets published.
5. Two systems for pathogen inactivation of platelets are CE marked and in routine use in several European countries and post-marketing surveillance data are indicative of clinical efficacy.

Remit

6. The working group will review the evidence base for pathogen inactivation of platelet technologies, will consider the relative benefits and disbenefits of the technologies available from all manufacturers and determine cost effectiveness of the introduction of PI of platelets.

7. Its remit includes:

    - Evaluating the evidence base for clinical efficacy of pathogen inactivated platelet components;
    - Determining the efficacy of the technology for inactivation of pathogens, including log kill of relevant bacteria, protozoa and viruses;
    - Assessing the efficacy of each individual technology;
    - Determining any additional benefits or disbenefits of PI, including discontinuation of any screening tests;
    - Reviewing relevant policies, usage and PMS data in other countries;
    - Evaluating the cost effectiveness of pathogen inactivation;
    - Evaluating the impact of any recommendations on UK Blood Services operational blood supply;
    - Recommendations for further research in this area
    - Determining recommendations for disseminating the outcome of the review.

8. In scope

    - Consideration of licensed PI technologies for platelets
    - Clinical efficacy of PI platelets
    - Clinical efficacy of PI technologies; log kill
    - Cost effectiveness in UK Blood Services
    - Operational implications

9. Out of scope
    - PI of other components
    - Systems not yet licensed in Europe

Terms of Reference

10. In formulating and communicating its advice, the working group will:

    - take account of the scientific evidence available, including the nature of uncertainties and assumptions used to reach conclusions;
    - take account of the infectivity risk of different tissues including the effects of processing;
    - take account of the differences in risk/benefit for different types of tissue and cellular products;
    - identify specific areas of research where further work is required to reduce uncertainty;
    - take account of the risk of policies being perceived as unfairly discriminatory;
    - consider the impact of its advice on all stakeholders in the supply chain, including but not exclusively donors, patients, the UK Blood Services and the wider NHS;
    - take account of the need to maintain the safety of cells and tissues under the remit of the Precautionary Principle;

- take account of any legal requirements;
- take account of any other SaBTO recommendations;
- be ultimately accountable to SaBTO.

Membership

11. Membership of the group will be as follows:

Name	Position	Role on Working Group
Dr Lorna Williamson (Chair)	SaBTO member (Medical Director of Blood Service) Medical and Research Director, NHSBT	Chair on behalf of SaBTO
Professor John Cairns	SaBTO member	Health Economist
Professor Tom Solomon	SaBTO member	Microbiologist/Bacteriologist / Virologist
Dr Mallika Sekhar	SaBTO member	Haematologist
Mrs Michelle Ashford	Assistant Director, NHSBT	Strategic Manufacturing Expertise
Dr Su Brailsford	Consultant in Epidemiology and Public Health, PHE/NHSBT	Epidemiology Expert
Dr Rebecca Cardigan	Head of Component Development, NHSBT	Pathogen Inactivation Expertise
Dr Sheila MacLennan	Transfusion Medicine, NHSBT	Transfusion Expertise
Dr Lynn Manson	Haematologist, SNBTS	Haematologist
Mr Steve Moore	Lead Quality Specialist, NHSBT	Quality Expert
Mr Andrew Parker	DH Analytical Team	Analytics
Dr Tyrone Pitt	Bacteriologist (PHE)	Bacteriology Expertise
Dr Simon Stanworth	Haematologist, NHSBT	Haematologist
Mr Vaughan Sydenham	Assistant Director of Finance, NHSBT	Financial Expertise
Dr Ines Ushiro-Lumb	Consultant Virologist, NHSBT	Virological Expertise
Mr Andrew Broderick	DH/NHS Blood and Transplant	Secretariat

Work programme

12. The work of the group is expected to be completed by December 2013, according to the following schedule:

Subgroup meeting	Milestone
6 September 2013	Definition of remit, delegation of workstream activities
4 October 2013	Review of initial outputs, determination of further information requirements

13 November 2013	Draft report for review
3 December	Full SaBTO Meeting – Presentation of Final Report

13. The working group may meet in person or by telecon.

14. Administrative issues will pass to the SaBTO Secretariat who will also maintain a document library.

15. Members of the Working Group are asked to claim expenses from their employing organisation. Where this is not possible, they can be claimed from DH. Expenses in relation to travel and subsistence necessarily incurred in carrying out the work of the Group are payable in line with DH rates for individuals who serve on committees. This is standard class for rail travel and economy class for air travel. Members of the Working Group are asked to make every effort to use public transport where possible, rather than taxis, although these may be used for local journeys (under 5 miles). Receipts must be submitted with claims.

16. Papers will be circulated no later than 7 days prior to any ordinary meeting.

Communications

17. The establishment of the working group was recorded in the minutes of the SaBTO meeting of 24 June 2014.

18. The Working Group will include stakeholders as detailed in section 8, and will consult relevant stakeholders. It will consider whether it is appropriate to conduct any other consultations when formulating its recommendations, although it is expected that sufficient expertise is included within the group. Unless specifically stated, members of the working group are not considered to be representatives of the organisations listed in section 9.

19. The recommendations of the Working Group will be published in a report and recommendation to SaBTO, with discussions and outcomes recorded in the public minutes of the meeting. A communications plan will be formulated.

20. This document will be appended to the report, so that the membership of the group is made public.

21. The Working Group will draw up a list of stakeholders that should be informed of SaBTO's recommendations and/or any decision by ministers.

Andrew Broderick
SaBTO Secretariat

Appendix 2

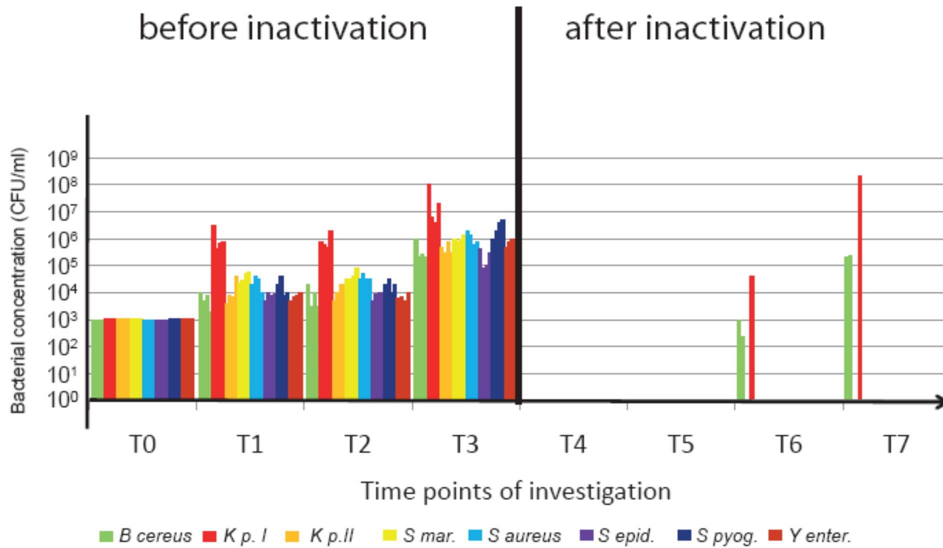
Table 22. EDQM survey - where data available

			EDQM survey		
Country	**IHN** [a]	**No adult dose platelets Tx**	**Pathogen Reduction** [b]	**Bacterial screening, culture**	**Pathogen reduction 2013**[c]
Austria	Y	38,711	No (2010)	76%	Approx 15 %
Belgium	Y	69,328	44%	56%	80 %
Bulgaria		5,700	1.8 %	1%	-
Canada	Y	Not reported	0	0	-
Croatia	Y	14,000	0	6%, 5%	-
Czech Rep.		31,600	0	1%	<5%
Denmark	Y	42,371	0	100%	5-10%
Estonia		6,034	0	100%	-
Finland	Y	41,659	0	6.3% only outdated platelets, 10%	-
France	Y	275,779	8%	0	5-10%
Germany	Y	437,014	0.07%	0	<5%
Greece	Y	-	0	0	5-10%
Ireland	Y	-	0	100%	
Italy	Y	214,599	-	9.5%	<10%
Latvia		6,131	2011, 0-	85%, 66%	-
Lithuania		14,646	2.7%	3%	-
Macedonia		14,119	-	1%	-
Malta	Y	1,256	0	? 5.9%	-
Moldova		9,083	0	? 2%	-
Montenegro		8,562	0	0	-
Netherlands	Y	56,000	0	100	
Norway	Y	-	2011 18%17%	78%, 76%	5-10%
Poland		90,533	Yes ?	0	20-30%
Portugal	Y	-	0	0, 100%	60%
Russia		452,196	2011 2%?	0	20%
Serbia		10,220	3.9%	5.2%, 0.03%	<5%
Slovak Rep		27,717	0	1%	-
Slovenia	Y	9,277	68%	2.6%	1 centre
Spain	Y	156,514	21	20	50%
Sweden	Y	42,553	2011 17%12	37, 44%	20%
Switzerland	Y	29,938	0	0	15-20%
UK	Y	240,106	0	0, 99%	0

[a] member of the International Haemovigilance Network
[b]survey data 2010 (or 08/09 where noted) shading 2009
[c]survey 2013, (Andrew Broderick personal communication)

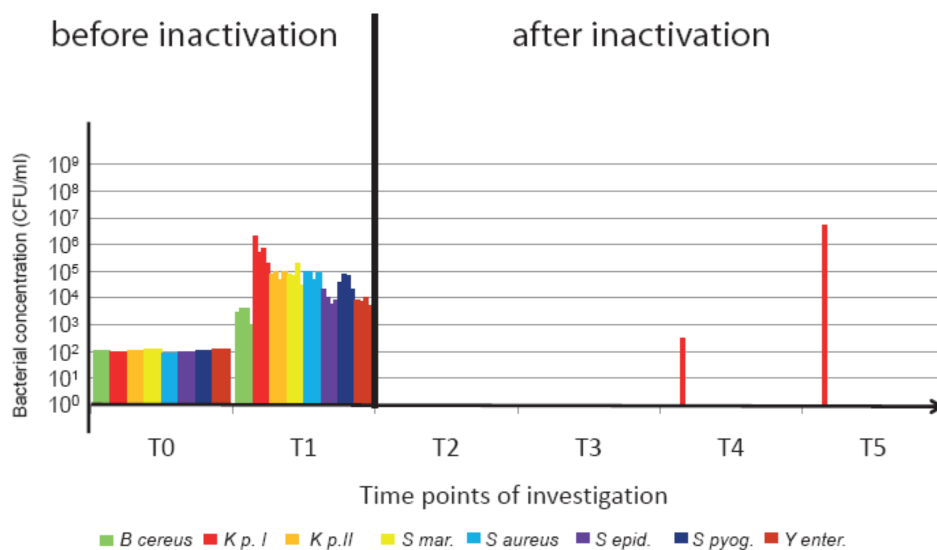
Bacterial regrowth

Serie B: Spiking concentration 1,000 CFU/bag whole blood samples



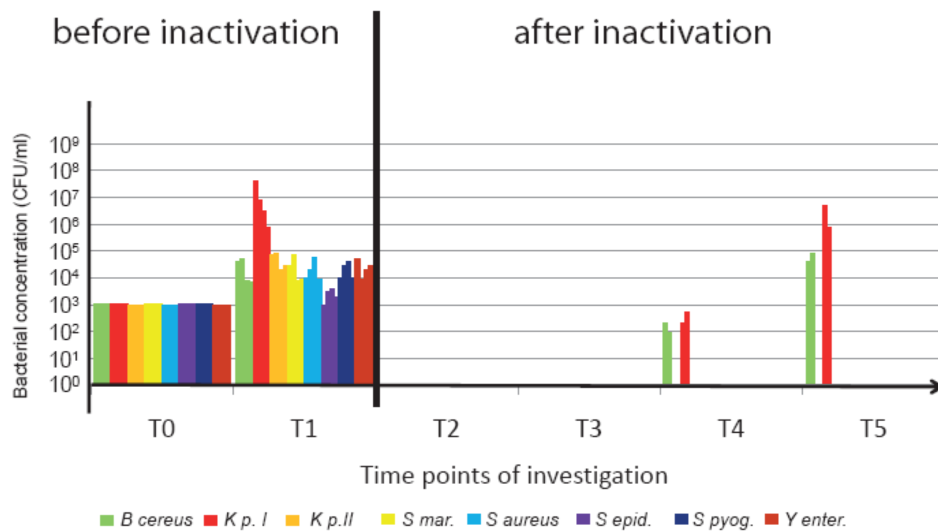
In 2 out of 4 cases B Cereus was detected on day 5 and day 7 after donation on blood agar plates as well as by BacT/ALERT. The concentration at T3 (before inactivation using Manufacturer A's system) was $1x10^6$ CFU/ml and $2.2x10^5$ CFU/ml, respectively.
In 1 out of 4 cases K pneumonae (hesse strain) was detected on day 5 and day 7 after donation. The bacterial concentration at T3 (before inactivation using Manufacturer A's system) was $1x10^8$ CFU/ml.

Serie A: Spiking concentration 100 CFU/bag pool platelets



In 1 out of 4 cases K pneumonae (hesse strain) was detected on day 5 and day 7 after donation on blood agar plates as well as by BacT/ALERT. The bacterial concentration at T1 (before inactivation using Manufacturer A's system) was $2x10^6$ CFU/ml.

Serie B: Spiking concentration 1,000 CFU/bag pool platelets



In 2 out of 4 cases B Cereus was detected on day 5 and day 7 after donation on blood agar plates as well as by BacT/ALERT. The bacterial concentration at T1 (before inactivation using Manufacturer A's system) was $4x10^4$ CFU/ml and $5x10^4$ CFU/ml, respectively.

In 2 out of 4 cases K pneumonae (hesse strain) was detected on day 5 and day 7 after donation on blood agar plates as well as by BacT/ALERT. The bacterial concentration at T1 (before inactivation using Manufacturer A's system) was $4x10^7$ CFU/ml and $8x10^6$ CFU/ml, respectively.

Appendix 4

ESTIMATING THE COST-EFFECTIVENESS OF PATHOGEN INACTIVATION OF PLATELETS

Note

SaBTO would like to thank the manufacturers for their co-operation with this review. Some of the detailed information they provided, while available to SaBTO to inform its consideration, is not included in this report as it is commercially confidential.

Some of the manufacturers do not agree with aspects of the methodology used in this modelling, considering it does not fully take into account the advantages of their product. However, SaBTO and the Department of Health believe the methodology was appropriate and fair.

The findings of SaBTO's review are based on the information and evidence available at the time. SaBTO is aware that considerable progress continues to be made in this field, and its recommendations include the initiation of a process by the UK Blood Services, taking account of this review, for evaluating new and existing technologies for the pathogen inactivation of blood components without a further SaBTO review of specific systems.

Purpose and overview of the Appendix

Section 7 provides an overview of the cost-effectiveness calculations. This Appendix provides a more detailed explanation of the methodology behind the calculations.

The methodology can be split into four stages:

- Estimating the cost of production of the basic platelet;
- Estimating the cost of screening or pathogen inactivating these units;
- Estimating the cost of treatment of infections and the number of life-years lost under each alternative; and finally
- Estimating the equity cost and cost-effectiveness of introducing pathogen inactivation.

In our analysis, we consider the costs of the five options:

1. As a baseline, we assume the current screening process, including bacterial screening;
2. Pathogen inactivation using the system provided by Manufacturer A, with a shelf life of 7 days;
3. Pathogen inactivation using the system provided by Manufacturer B, with a shelf life of 7 days;
4. Pathogen inactivation using the system provided by Manufacturer B, with a shelf life of 5 days; and
5. Pathogen inactivation using the system provided by Manufacturer C, with a shelf life of 5 days.

Following the recommendation at SaBTO's September meeting, we assume that all platelet units will be suspended in Platelet Additive Solution.

Inevitably, there are uncertainties in these calculations. Two of these we have covered by presenting results for a variety of options:

1. *Procurement of platelets.* We do not yet know what proportion of platelets will be procured by apheresis, and so our analysis considers three possible options (20%, which has been determined as the absolute minimum level; 35% and 50%).
2. *Impact on demand:* The clinical group of the SaBTO Pathogen Inactivation of Platelets Working Group also suggested that the introduction of pathogen inactivation may lead to an increase in the demand for platelet units of up to 5%. For this analysis, we consider the two extremes of a 0% and a 5% increase.

This note works through these four stages for one of the scenarios (an apheresis level of 35% and a 5% increase in the demand for platelets) before presenting the cost-effectiveness calculations for all of the different combinations.

Finally, it considers the impact of two further areas of uncertainty by carrying out sensitivity analysis:

1. Infectivity of vCJD. The analysis assumes that the platelets and plasma in a normal whole blood donation that is contaminated with vCJD will contain 3 Infectious Doses (IDs). Our main analysis assumes that all of these IDs are in the plasma. This is the least disadvantageous for pathogen inactivation, but experts advise that we cannot assume that there is no infectivity in the platelets. Our sensitivity analysis therefore presents corresponding results if there are 0.25 IDs in the platelets and 2.75 in the plasma. (Note that neither bacterial screening nor pathogen inactivation affects the transmission of vCJD, and so there is only an impact in the scenario where there is an increase in the number of units of platelets issued); and
2. *Effectiveness of pathogen inactivation.* Our main analysis assumes that the effectiveness of pathogen inactivation of bacteria is the same as that of bacterial screening. Our sensitivity analysis presents corresponding results if the proportion of failures of pathogen inactivation is halved, and if it is doubled.

Estimating the cost of production

We assume that around 316,000 units of platelets will be issued by Blood Services to the NHS in the UK. Under the current procedure, we assume that wastage would be 9.32%[33]. For options 2 and 3 with a shelf life of 7 days, we anticipate that introducing pathogen inactivation would reduce the production time by a day, cutting the wastage rate by 0.75%[34]. For options 4 and 5 with a shelf life of 5 days, we anticipate that the wastage rate will be increased by 1% as the number of days for which units will be available for issue will be reduced by one[2].
In this scenario we assume that a further 5% of units will need to be produced where pathogen inactivation is introduced. If we assume that 35% of units will be procured by apheresis, Table 23 derives the production costs for the different options.

[33] Wastage rate of 9.32% provided by NHSBT finance, 5 July 2013.
[34] Wastage rate adjustments confirmed by NHSBT finance, 15 November 2013.

Table 23: numbers of units of platelets produced per year

	Baseline	PI, 7day shelf life	PI, 5 day shelf life
Units issued per year	316,000	316,000	316,000
Wastage rate	9.32%	8.57%	10.32%
Increase in demand	0	5%	5%
Units produced per year	348,478	362,901	369,982
Apheresis units per year	121,967	127,015	129,494
Pooled units per year	226,511	235,885	240,488
Production costs per year	£21.8m	£22.7m	£23.1m

Estimating the cost of screening/pathogen inactivation

At present, units incur the costs of bacterial screening, plus staff costs and a TSCD wafer. We assume that the staff cost and TSCD wafer costs for all pathogen inactivation systems would be the same as for bacterial screening. We estimate that 0.5% of apheresis units and 0.37% of pooled units produce an initial positive result[35] and require confirmatory testing; they will also trigger a recall of the units and, in the case of a pooled unit, the four corresponding red cells units, all of which incur additional costs. We would expect that all of the four red cell units would need to be replaced. However, we estimate that 41% of recalled units have already been issued, and that 64% of those issued have already been transfused. As a result of this, we estimate that around 74% of recalled platelet units will need to be replaced.

The clinical group of the Pathogen Inactivation Working Group has advised that irradiation would not be needed if pathogen inactivation were implemented, and so we include the cost of irradiating 51% of units as a cost of the current system.

Table 24 presents the total cost of screening under the current system.

Table 24: Costs per year of bacterial screening and irradiation under the current production system

Units produced per year	348,478
Units for confirmatory testing	1,438
Units for irradiation	177,724
Total baseline screening cost	£3.8m

The cost of using each manufacturer’s pathogen inactivation system is different, and not only because the prices vary. A single pack for manufacturer A can be used to

[35] NHSBT/PHE Epidemiology Unit, Feb 2011 – June 2013

process a single or double apheresis donation, although a triple apheresis donation would require two packs. In addition, manufacturer A indicates that between 10 and 12 illuminators will be needed (we have assumed 11), which will require annual maintenance. Manufacturer B, on the other hand, suggests that a single pack could be used for processing all sizes of donation. However, the clinical group of the working group have recommended that we assume that two packs would be needed to process a triple apheresis donation and a single pack could be used for other donations. Manufacturer B's annual illuminator maintenance costs are also different from manufacturer A's. Manufacturer C indicates that packs will need to be pathogen inactivated separately, and that maintenance will be required for each of fifteen UV machines.

In calculating costs, we assume that 1.5% of apheresis units are collected as single units, 76% as double units and 22.5% as triples. Table 25 presents the numbers of different types of donation to be processed.

Table 25: Annual costs of Pathogen Inactivation

	Manuf'r A	**Manuf'r B (7 day)**	**Manuf'r B (5 day)**	**Manuf'r C**
Apheresis units	127,015	127,015	129,494	129,494
Apheresis singles	1,892	1,892	1,929	1,929
Apheresis doubles	96,478	96,478	98,360	98,360
Apheresis triples	28,646	28,646	29,205	29,205
Pooled units	235,885	235,885	240,488	240,488
Total annual cost	Ranges from £8.0m to £16.1m			

Estimating clinical impact

The introduction of pathogen inactivation would also have an impact on the likelihood of transfusion-transmitted infection. We have restricted our modelling to bacterial infection and, if the demand does increase, to vCJD.

For bacterial infections, we consider all bacteria other than Gram positive rods-skin flora, which are considered unlikely to cause harm. Up to the end of June 2013, NHSBT had 55 apheresis units of platelets confirmed positive for relevant bacteria, and 27 pooled units from testing of 498,801 and 93,051 units, respectively. This suggests a prevalence of around 0.01% in apheresis units and 0.03% in pooled units. If we assume that around 245,000 units of platelets were issued each year from 2003 to 2010 (the last full year before bacterial screening was introduced), and that 80% of these units were procured by apheresis, then assuming the same prevalence we would expect around 290 units would have been issued which contained relevant bacteria.

Over this period, 4 deaths, 10 individuals with major morbidity and 2 individuals with minor morbidity were reported to Serious Hazards of Transfusion resulting from transfusion-transmitted bacterial infection. If we assume that all 16 individuals required treatment, then this gives a probability of around 5.5% that an infected unit that is not

successfully screened or inactivated would result in a patient requiring treatment, and a probability of around 1.4% that the infection will result in death.

We estimate that the cost of treating a bacterial infection is around £9,200[36], and that preventing a death resulting from bacterial infection would save 9.1 life-years[37].

We have assumed that bacterial screening will identify 74 out of 75 units infected with relevant bacteria (roughly equivalent to missing one relevant bacteria-infected unit per 500,000 platelet units issued), and that pathogen inactivation will render 74 out of 75 infected units clinically safe. However, with bacterial screening, we again estimate that 41% of recalled units have already been issued, and that 64% of those issued have already been transfused.

Table 26 presents the calculations for the clinical impact of bacterial infections under the current bacterial screening and pathogen inactivation.

To estimate the impact of extra vCJD infections resulting from extra units being transfused, we have used the results from September 2013 to inform the decision regarding apheresis. By assuming that all future cases result from transfusions in the next 20 years, we estimate the expected number of cases to be of the order of 5 per extra million units of platelets transfused and that each case results in the loss of 14 symptom-free life-years when discounted.

Table 26: Cost of treatment and the number of life-years lost per year as a result of transfusion-transmitted bacterial and vCJD infections, assuming 35% apheresis and a 5% increase in demand resulting from pathogen inactivation

	Baseline	Pathogen inactivated
Apheresis units per year	121,967	127,015
Pooled units per year	226,511	235,885
Units with bacterial infection donated per year	72	75
Units with bacterial infection issued per year	20	1
Cases requiring treatment	1.1	0.1
Cost of treatment of bacterial infections (per year)	£10.2k	£0.5k
Deaths resulting from bacterial TTI	0.3	0.0
Life-years lost – bacterial	2.5	0.1
vCJD cases per year	1.6	1.6
Life-years lost – vCJD	21.9	23.0
Total life-years lost	24.4	23.1

[36] This is calculated by uplifting an estimate of £5,400 data from a 1998 study into Healthcare Acquired Infections into 2012/13 terms using the Hospital and Community Health Services Pay & Prices index, and then into 2013/14 terms using the Consumer Prices Health Index.
[37] Using data on six-year survival of platelet transfusions from the Epidemiology and Survival of Transfusion Recipients (EASTR) study.

Estimating the equity cost and cost-effectiveness

SaBTO has adopted a “safety framework” to inform its decisions about the introduction or withdrawal of safety measures. Under this framework, we consider the cost-effectiveness of a measure for recipients aged 60 or under. A separate “equity cost relating to the provision for over-60s” is also calculated, where a value is attached to the life-years saved among these older patients and subtracted from the cost of implementing the measure for the patient group. We therefore need to identify the costs and life-years saved for the two groups separately.

We estimate that patients aged over 60 receive around 39% of platelets[38] that are transfused, and therefore account for the same proportion of the costs. We also assume that they will account for the same proportion of bacteria-related deaths[39] and around 1.2% of projected clinical vCJD cases. We also estimate that 3.8 life-years per bacteria-related death and 0.2 life-years per clinical case of vCJD are lost in this age-group.

Table 27 shows the resulting estimates of the number of life-years saved by pathogen inactivation, and Table 28 the resulting equity cost and cost-effectiveness calculations.

Table 27: Number of life-years lost per year among patients up to 60 years of age as a result of transfusion-transmitted bacterial and vCJD infections, assuming 35% apheresis and a 5% increase in demand resulting from pathogen inactivation

	Baseline	Pathogen inactivated
Deaths resulting from bacterial TTI	0.3	0.0
Deaths resulting from bacterial TTI - over 60s	0.1	0.0
Life-years lost from bacterial TTI - over 60s	0.4	0.0
Total life-years lost - over 60s	0.4	0.0
Total life-years lost	24.4	23.1
Total life-years lost - under 60s	24.0	23.1
Life-years saved by PI		0.9

Note: life-years lost among the over 60s from vCJD are not shown as they are under 0.005.

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[38] Wells AW, Llewelyn CA, Casbard A, *et al* (2009): The EASTR Study: indications for transfusion and estimates of transfusion recipient numbers in hospitals supplied by the National Blood Service. *Transfusion Medicine*, 2009, 19, 0-0. (data on transfusions to patients aged over 60 was provided by A. Wells)

[39] We note that this is likely to be an underestimate, resulting in more life-years remaining to the under-60s and a more favourable cost-effectiveness calculation.

Table 28: Equity costs and costs per life-year saved for patients aged under 60 for alternative pathogen inactivation systems, assuming 35% apheresis and a 5% increase in demand resulting from pathogen inactivation

	Baseline	Manuf'r A	Manuf'r B (7 day)	Manuf'r B (5 day)	Manuf'r C
Production cost/year	£21.8m	£22.7m	£22.7m	£23.1m	£23.1m
Screening or PI cost/year	£3.8m	Range from £8.0m to £16.1m			
Total cost	£25.5m	Range from £30.7m to £39.2m			
Total cost of PI		Range from £5.1m to £13.6m			
% units over 60		39%	39%	39%	39%
Equity cost		Range from £2.0m to £5.3m			
Cost for under-60s/year		Range from £3.1m to £8.3m			
Life-years saved by PI		0.9	0.9	0.9	0.9
Cost/life-year (£m)		Range from £3.4m to £9.1m			

Note: Clinical treatment costs are below £50,000 and so not shown in the table. Repeating these calculations for the alternative scenarios with 50% and 20% apheresis, and with no extra demand for platelets, gives the following table for cost per life-year saved.

Table 29: Cost per life-year saved for the alternative pathogen inactivation systems, with alternative levels of apheresis and increase in demand

% units by apheresis	Increase in platelet demand	Manuf'r A	Manuf'r B (7 days)	Manuf'r B (5 days)	Manuf'r C
20%	0%	Range from ££1.0m to £3.2m			
35%	0%	Range from £1.1m to £3.6m			
50%	0%	Range from £1.3m to £4.0m			
20%	5%	Range from £2.6m to £7.1m			
35%	5%	Range from £3.4m to £9.1m			
50%	5%	Range from £4.7m to £12.2m			

The table shows that the cost per life-year saved is at least £1m for each option, under each scenario, which is significantly higher than the usual cost-effectiveness threshold of £25,000 per Quality-Adjusted Life-Year (QALY) saved.

The figures presented so far relate to the running costs that we have been able to estimate. They do not include the cost of the actual recall process; the benefit of not needing to have a separate product line for irradiated platelets; the hospitals' costs for handling the extra units if demand does increase; and the benefits from identifying donors' clinical conditions as a result of bacterial screening. The first two of these will tend to improve the cost-effectiveness of pathogen inactivation while the last two will tend to reduce the cost-effectiveness.

Capital costs

The calculations also do not include the capital costs of pathogen inactivation. Manufacturer A says that between 10 and 12 illuminators would be needed; Manufacturer B that 15 illuminators would be needed; and Manufacturer C that 15 UV machines would be required. We also understand that the process for Manufacturer A would require incubators, although we do not know what investment this would require. We understand that there are no corresponding capital costs for the current bacterial screening process as the machines are hired.

Sensitivity analysis

Variant CJD infectivity

The figures in the calculations above assume that all of the 3 IDs of infectivity in the platelets and plasma in a whole blood donation relate to the plasma. This assumption is now subject to some question. As a result, we also consider the alternative of 0.25 of the IDs being in the platelets and 2.75 in the plasma.

The risk of vCJD transmission is not affected by bacterial screening or pathogen inactivation, and will therefore only change if there is an increased demand for platelets. Repeating the calculations with the alternative vCJD assumption, where the number of cases changes from around 5 to around 8 per million units, gives the following revised version of Table 29.

Table 31: Cost per life-year saved for the alternative pathogen inactivation systems, with alternative levels of apheresis and vCJD infectivity, assuming a 5% increase in demand

<table>
<tr><th>% units by apheresis</th><th>Increase in platelet demand</th><th>Manuf'r A</th><th>Manuf'r B (7 days)</th><th>Manuf'r B (5 days)</th><th>Manuf'r C</th><th>vCJD infectivity</th></tr>
<tr><td>20%</td><td>5%</td><td colspan="4">Range from £2.6m to £7.1m</td><td rowspan="3">0ID in platelets per WB donation</td></tr>
<tr><td>35%</td><td>5%</td><td colspan="4">Range from £3.4m to £9.1m</td></tr>
<tr><td>50%</td><td>5%</td><td colspan="4">Range from £4.7m to £12.2m</td></tr>
<tr><td>20%</td><td>5%</td><td colspan="4">Range from £6.9m to £18.8m</td><td rowspan="3">0.25ID in platelets per WB donation</td></tr>
<tr><td>35%</td><td>5%</td><td colspan="4">Range from £12.1m to £32.1m</td></tr>
<tr><td>50%</td><td>5%</td><td colspan="4">Range from £35.4m to £92.1m</td></tr>
</table>

Effectiveness of pathogen inactivation

Figures in the calculation above assume that pathogen inactivation is as effective at rendering bacteria clinically safe as bacterial screening is at detecting their presence, effective for 74 infected bags out of 75. This is not based on clinical evidence, and so we investigate the impact of changing this assumption on the cost-effectiveness of pathogen inactivation.

Table 32a shows the cost per life-year saved for the alternative levels of apheresis and increase in demand, but changing the assumption so that pathogen inactivation is effective for 149 bags out of 150 (halving the “failure” rate) and Table 32b shows the figures where it is assumed to be effective for 73 bags out of 75 (doubling the “failure” rate).

Table 32: Cost per life-year saved for the alternative pathogen inactivation systems, with alternative levels of apheresis and increase in demand, and alternative effectiveness assumptions

Table 32a – “failure” rate halved

% units by apheresis	Increase in platelet demand	Manuf'r A	Manuf'r B (7 days)	Manuf'r B (5 days)	Manuf'r C
20%	0%	Range from £1.0m to £3.1m			
35%	0%	Range from £1.1m to £3.5m			
50%	0%	Range from £1.2m to £3.9m			
20%	5%	Range from £2.5m to £6.8m			
35%	5%	Range from £3.2m to £8.6m			
50%	5%	Range from £4.4m to £11.4m			

Table 32b – “failure” rate doubled

% units by apheresis	Increase in platelet demand	Manuf'r A	Manuf'r B (7 days)	Manuf'r B (5 days)	Manuf'r C
20%	0%	Range from £1.0m to £3.3m			
35%	0%	Range from £1.2m to £3.7m			
50%	0%	Range from £1.3m to £4.3m			
20%	5%	Range from £2.9m to £7.9m			
35%	5%	Range from £3.9m to £10.3m			
50%	5%	Range from £5.5m to £14.1m			

Comparing these two tables with table 29, we see that this level of change to the assumed effectiveness of pathogen inactivation does have an effect on the cost per life-year, but does not affect it sufficiently to bring it close to the standard threshold of £25,000.