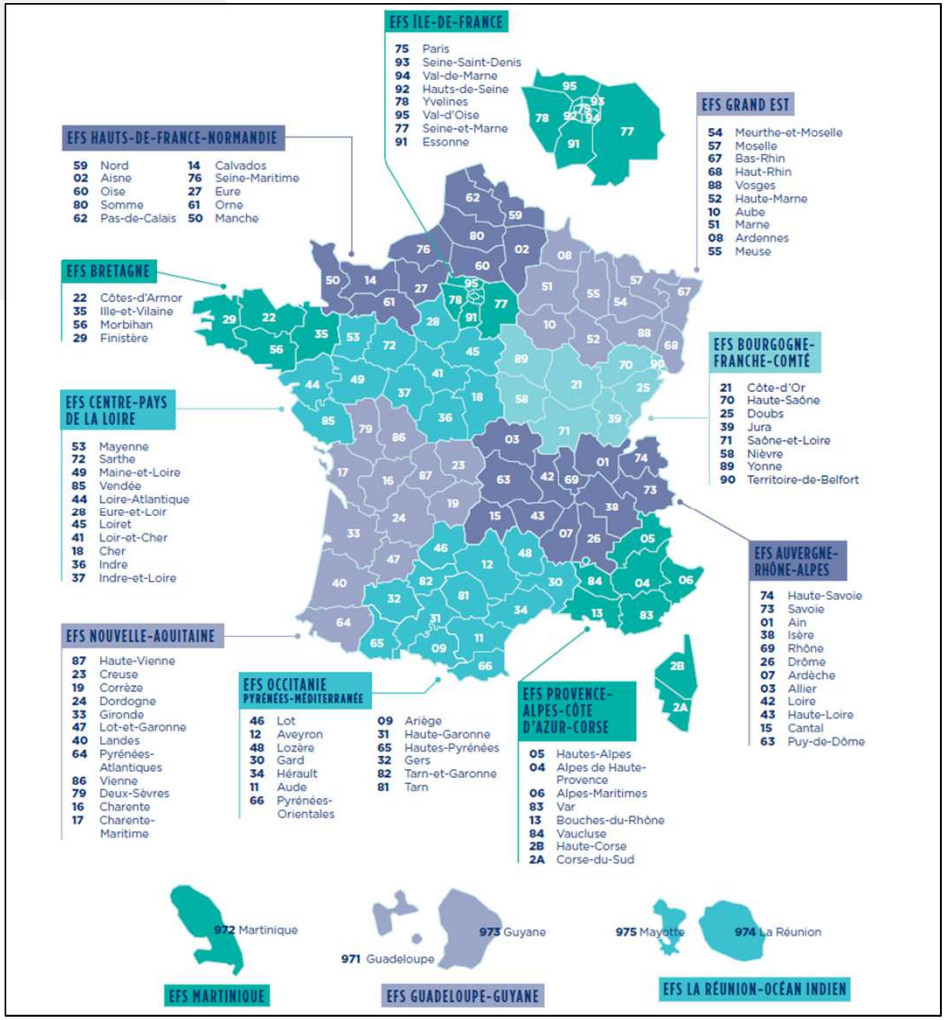
Pathogen reduced platelets in France and transfusion-transmitted infection risk: the French experience after 6 years of use

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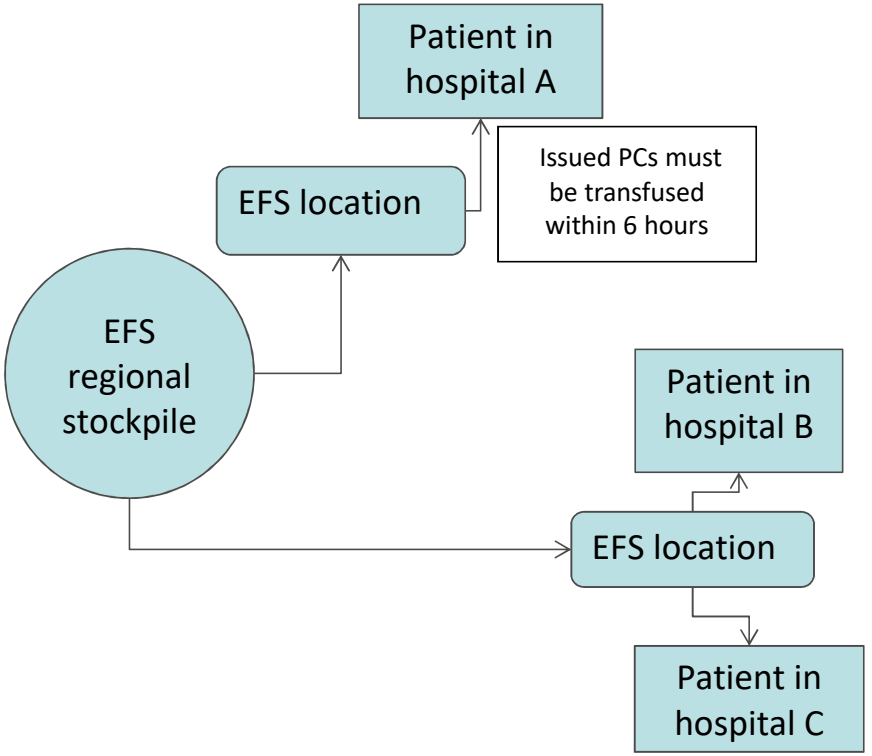


Conflict of interest disclosures:
None other than being employed by the Etablissement Français du Sang (EFS), the French transfusion public service in charge of collecting, procession and issuing blood components in France

Etablissement Français du Sang: the french transfusion public service



A large majority of blood components are directly issued by EFS to the clinical ward



Background:

- **Pathogen reduction (PR) technology** reduces the risk of **transfusion-transmitted infections (TTI**), notably transfusion-transmitted **bacterial infection** associated with platelet concentrate (PC).
- Pathogen reduction (**Intercept™, amotosalen** + UVA treatment, Cerus corporation) was **introduced for all PC in France** in November 2017.
- Before November 2017, **no bacterial detection in PC** was in place, while ≈ 8% PC underwent PR (since 2006).
- **Other measures in place to prevent TTI** included donor screening, skin asepsis, derivation of the first 35–40 mL of donated blood, donation testing for relevant pathogens, blood component quarantine upon post-donation information suggesting an infectious risk and careful visual inspection of the blood component at time of issuing (notably checking for appropriate swirling in PC).
- Reporting to the competent authority (ANSM) through a dedicated national website (e-FIT) health of blood donations found positive for pathogens as well of TTI is **mandatory.**

Aim:

- To assess the impact of moving to 100% PR PC in France on **the risk of PC - mediated TTI**.

Methods:

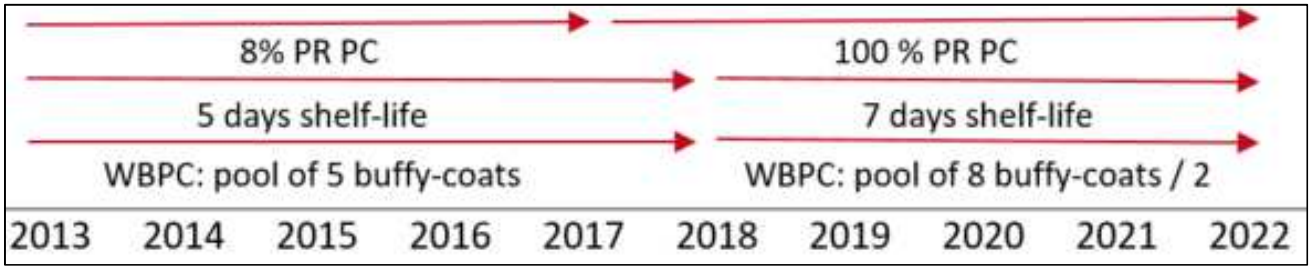
- PC - mediated TTI were **compared before and after implementation of 100% PR PC**
- Study period: 2013 to 2023

Blood donation testing :

- All blood (and plasma/platelet) donations are tested for **HIV** (individual donation–nucleic acid testing [ID-NAT] and Ab), **HBV** (ID-NAT, HBsAg and anti-HBcAb), **HCV** (ID-NAT and Ab), **HTLV-1** (Ab, restricted to first-time donors in mainland France since April 2019), **syphilis** (anti-treponemal Ab), **HAV** and **Parvovirus B19** (96 pool NAT, for the purpose of plasma for fractionation).
- **HEV** (six pool NAT) screening has been introduced for all donations in 2023. Beforehand, a fraction of plasma intended for transfusion (quarantine or pathogen reduced) to high-risk patients (chronic liver disease, immunosuppression) was screened for HEV-RNA (since 2013).
- In case of an **arbovirus** outbreak (notably autochthonous human cases of **West Nile**, **Zika** or **Dengue** infections), and depending on the geographic spread as well as the number of cases, donor deferral or specific NAT testing is introduced for whole blood donations in the involved locations. Apheresis PR PC and apheresis plasma intended for fractionation are not subject to these restrictions.
- Prevention of transfusion-transmitted **Malaria** and **Chagas** infections is ensured by targeted donor deferral and Ab testing

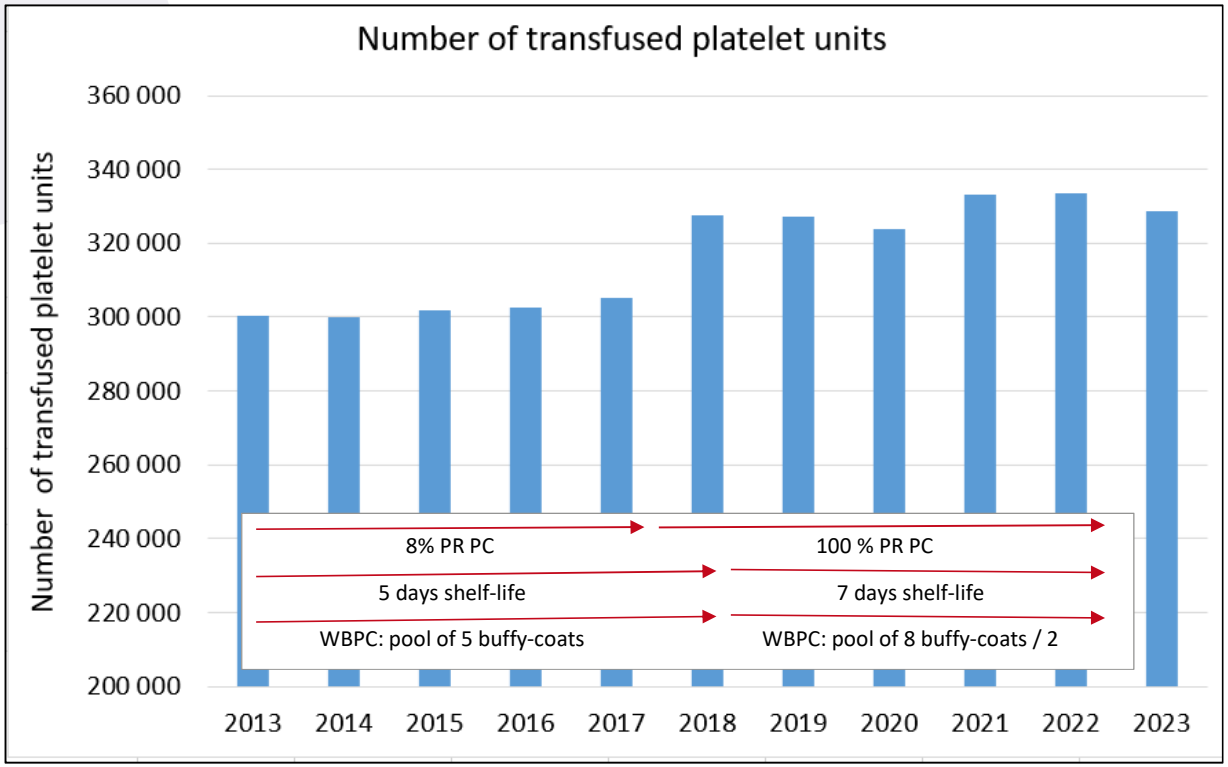
Platelet concentrate manufacturing

- All PC in additive solution since over 15 years
- Increasing proportion **of whole blood-derived pooled PC** (WBPC)(vs **apheresis PC** (APC)), from 51% (2013) to 72% (2022)
- **Introduction of pathogen reduction** (Intercept, Cerus corporation) for all PC in 2017 (8% beforehand)
- To reduce costs associated with PC processing:
  - **Extension of PC shelf-life from 5 to 7 days** : introduced in 2018, generalized in 2019.
  - **Increased WBPC pool size from 5 to 8 donations (buffy-coats)**, before being **divided in 2 units**: introduced in 2018, 30% in 2018 up to 96.5% in 2022
  - **Divided APC** introduced in 2018, up to 20% in 2022.

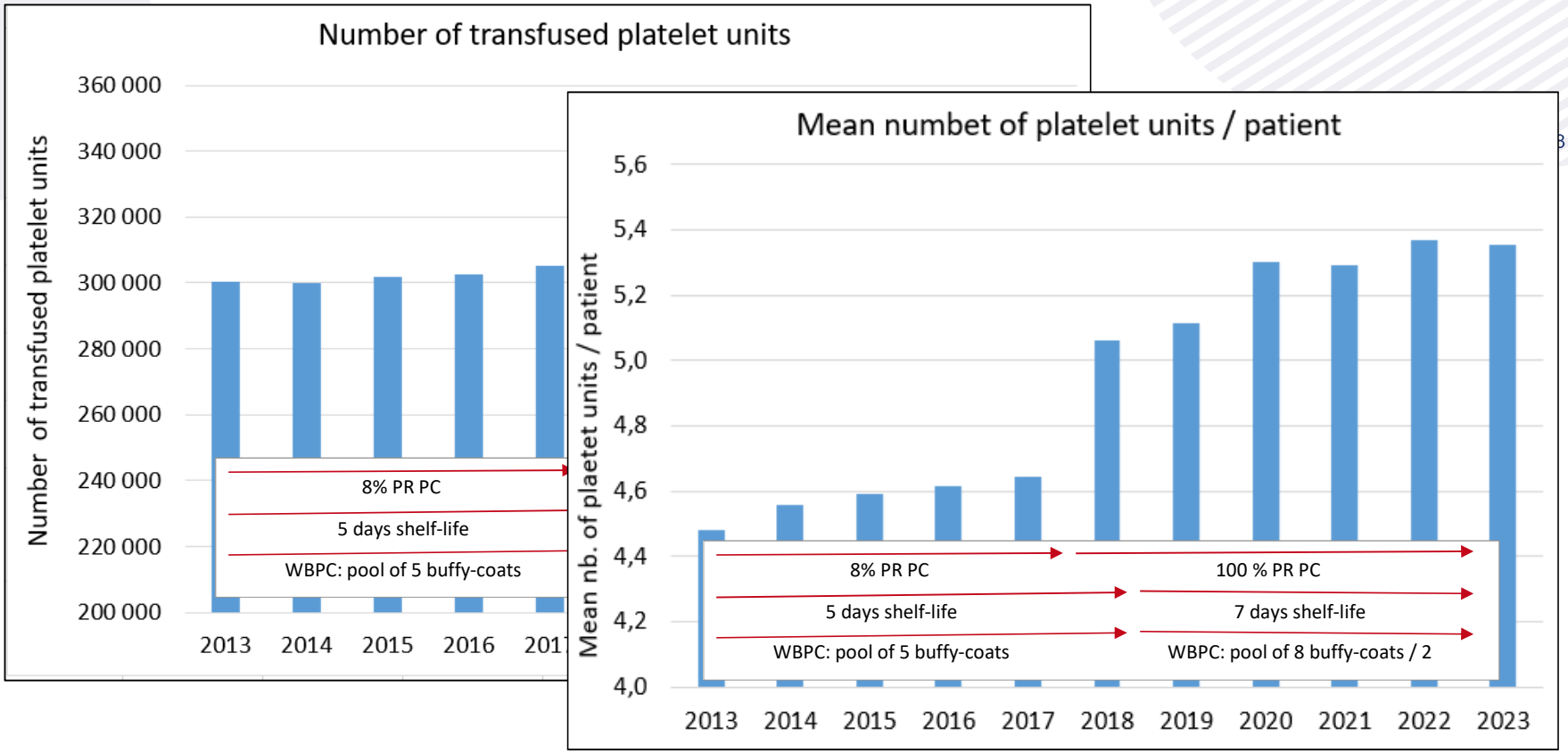


- In 2024, transfused PC comprise **> 40% day 6 or day 7 PC**
- **Expiration rates decreased**:
  - from 2.02 % (2017) to 1.06% (2021) for apheresis PC
  - from 4.71% (2017) to 1.40% (2021) for WBPC

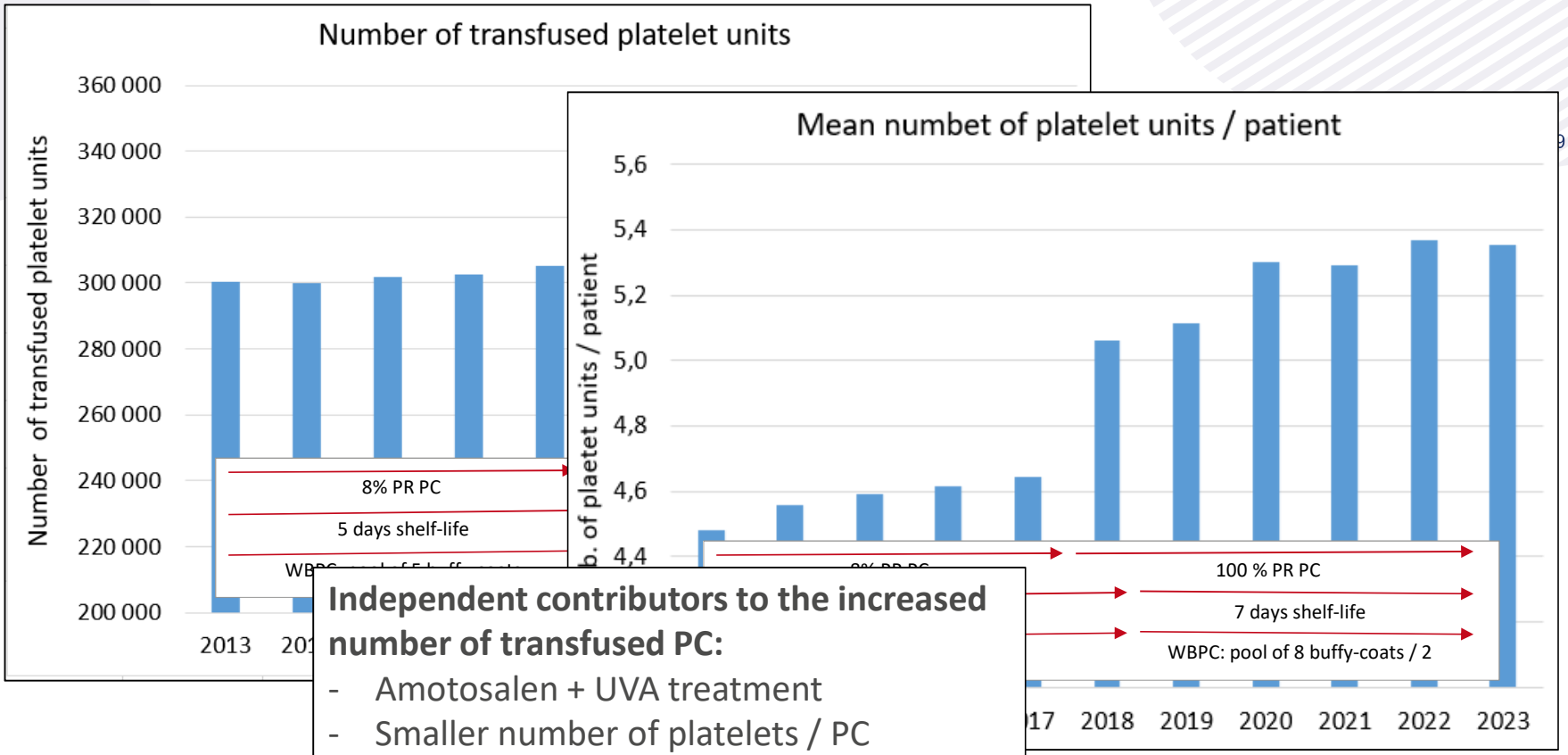
Platelet concentrate transfusion 2013 - 2023



Platelet concentrate transfusion 2013 - 2023



Platelet concentrate transfusion 2013 - 2023



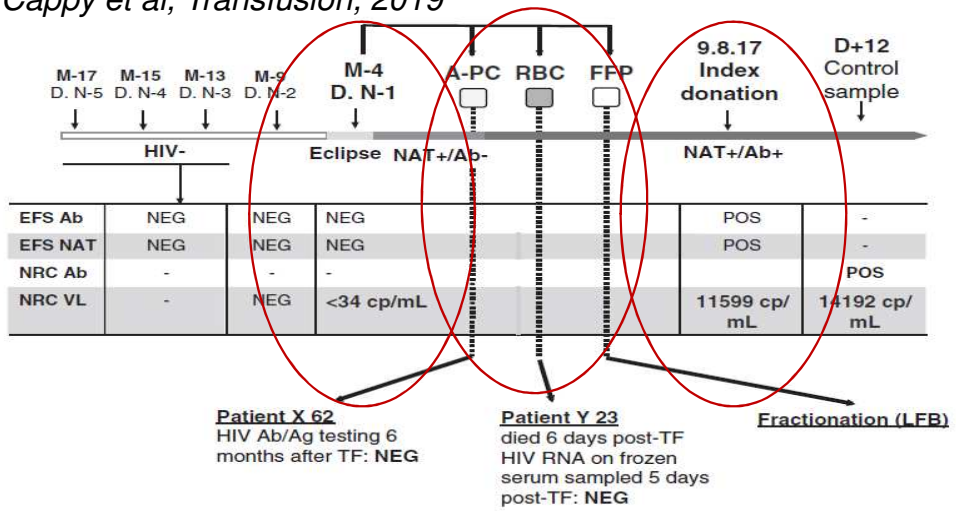
Independent contributors to the increased number of transfused PC:

- Amotosalen + UVA treatment
- Smaller number of platelets / PC
- Extended PC shelf life

Platelet concentrate - related transfusion transmitted viral infections

- No PC-related transmission of **HIV, HBV, HBC and HTVL-1**
  - Transfusion of blood components (RBC and PR-PC) from an **HIV**-infected donor (ID NAT negative upon initial screening, < 34 cp/ml upon repeat testing) in 2017

Cappy et al, Transfusion, 2019



Platelet concentrate - related transfusion transmitted viral infections

- No PC-related transmission of **HIV, HBV, HBC and HTVL-1**
- **HEV** PC-related transmission occurred before and after PR implementation (*Gallian et al, Transfusion Med Rev, 2018*), 1 to 5 reported TT HEV infections / year

Platelet transfusion – related HEV infection

Year	Blood component (pool size)	N=	Severity	Imputability
2013	WBPC (5)	1	1	3
	APC	1	1	2
2014	APC	4	1 / 1 / 1 / 2	3 / 2 / 3 / 2
	WBPC (5)	1	1	3
2015	WBPC (5)	1	1	3
	APC	1	2	2
	PR WBPC (5)	1	1	3
2016	WBPC	1	2	3
	APC	1	1	3
2017	WBPC (5)	2	2	3
2018	PR WBPC (5)	1	1	3
2019	PR WBPC (8)	4	2 / 1 / 1 / 2	3
	PR APC	1	2	3
2020	PR WBPC (5/8/8/*)	4	1 / 1 / 1 / 2	3 / 3 / 3 / 2
2021	PR WBPC (8/8/*)	3	1	3 / 2 / 2
2022	PR WBPC (8)	1	1	3

Severity grading:
1: not severe
2: severe
3: life-threatening
4: death

Imputability grading:
1: possible
2: probable
3: certain

Data source: ANSM / EFS
WBPC: pooled whole blood – derived platelet concentrate; PR: pathogen reduced APC: apheresis pooled platelet concentrate
*: undetermined, probably 8

Platelet concentrate - related transfusion transmitted viral infections

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		1	1	3
		1	2	2
		1	1	3
		1	2	3
		1	1	3
		2	2	3
		1	1	3
2019	PR WBPC (8)	4	2 / 1 / 1 / 2	3
	PR APC	1	2	3
2020	PR WBPC (5/8/8/*)	4	1 / 1 / 1 / 2	3 / 3 / 3 / 2
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Severity grading:
1: not severe
2: severe
3: life-threatening

Among red blood cell transfusion - related HEV infection cases:
- Grade 4, probable imputability
- Chronic hepatitis E, multiple organ failure in a heart transplant recipient

Belliere J et al, Transpl Infect Dis 2017
Gallian et al, Transfusion Med Rev, 2019

Data source: ANSM / EFS
WBPC: pooled whole blood – derived platelet concentrate; PR: pathogen reduced APC: apheresis pooled platelet concentrate
*: undetermined, probably 8

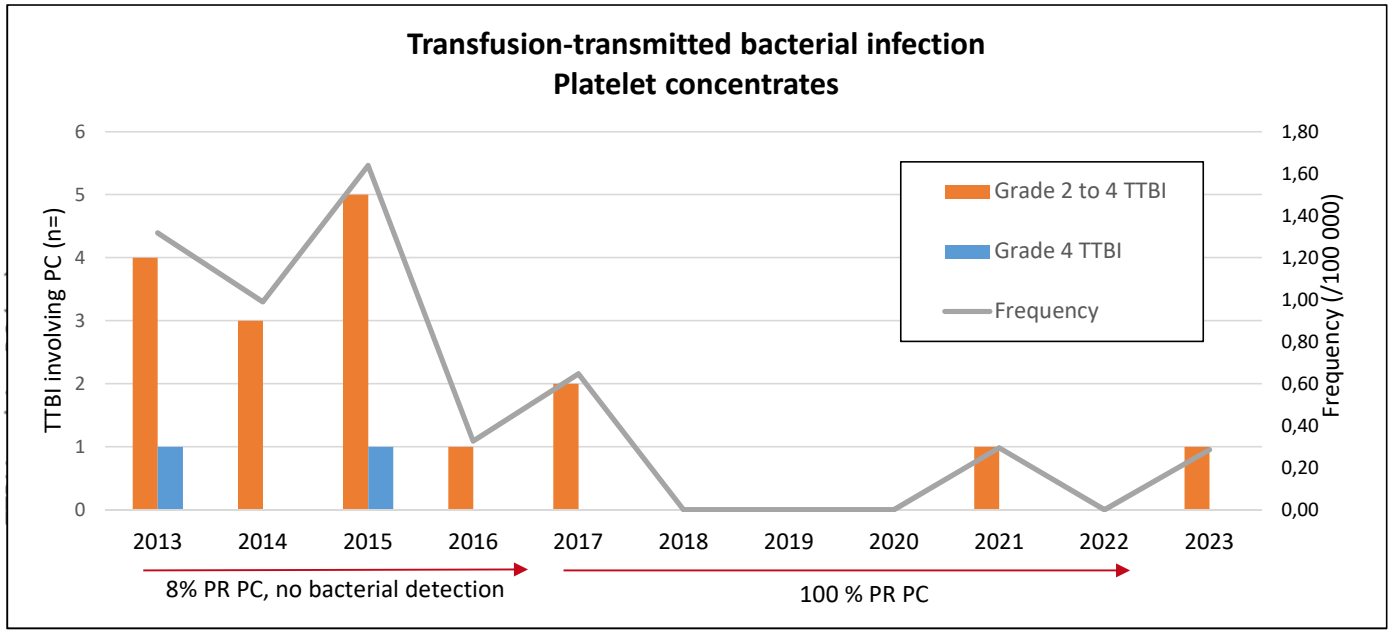
Platelet concentrate - related transfusion transmitted viral infections

- No PC - related transmission of **HIV, HBV, HCV or HTVL-1**
- **HEV** virus PC-related transmissions before and after PR implementation (*Gallian et al; Transfusion Med Rev, 2018)*
- Isolated **HAV** PC-related transmission during outbreaks (n=2, involving a non-PR PC and a PR-PC) (*Gallian et al, Eurosurveillance, 2018 and 2019*)
- No PC - related transmission of **arbovirus** or **parvovirus** (or Chagas, Syphilis, …)

Platelet concentrate - related transfusion transmitted bacterial infections

- **PC mediated TTBI annual occurrence prior to 100% PR PC implementation** was **n=3 (s.d.:1)/year** (all non-PR PC, n=15, frequency: 1/93 600 PC between 2013 and 2017). A fatal outcome occurred in 2 patients (2/15)(three grade 1, two grade 2, eight grade 3, two grade 4).
- **Since implementation of 100% PR PC in 2017, two TTBI have been reported (less than 1/year)**, involving Bacillus cereus (D4 PR APC, grade 3) and Bacillus hominis (D3 PR WBPC, grade 2)
- **Frequency**: 1/987 000 transfused PR PC between 2018 and 2023 vs 1/93 600 transfused non PR PC between 2013 and 2017)(p<0.001).

Severity grading:
1: not severe
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3: life-threatening
4: death



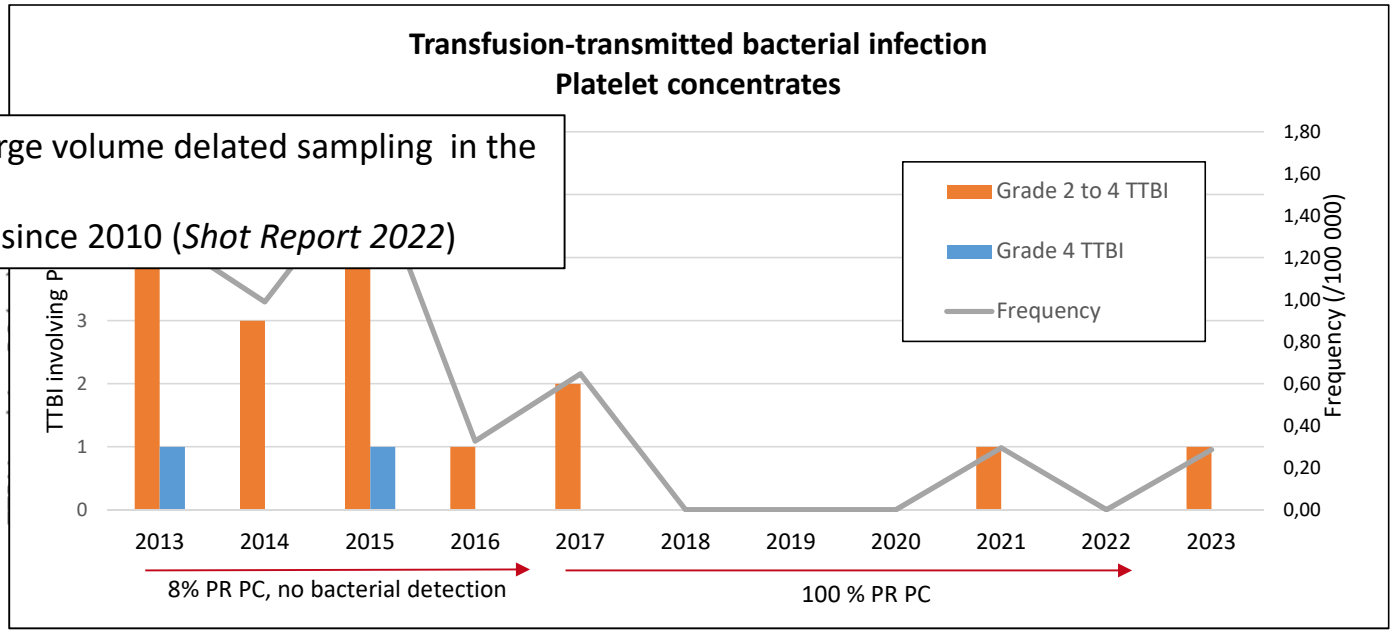
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Bacterial culture with large volume delated sampling in the UK:

- One PC-related TTBI since 2010 (*Shot Report 2022*)

3: life-threatening
4: death



Occurrence of transfusion-transmitted bacterial infection near-miss

- **Three PR PC** quarantined because of a negative swirling test were found to **harbor bacteria**:
  - day 6 WBPC in 2021 (*Bacillus cereus* and *Staphylococcus epidermidis*). The recipient of the second sub-unit died on day 2 of a cause felt to be unrelated to the transfusion
  - day 7 APC in 2022 (*Staphylococcus aureus*).
  - day 4 WBPC in 2023 (*Bacillus hominis*)(second sub-unit involved in the 2023 TTBI)
- Inspection of the containers did not reveal leaks. Amotosalen plus UVA treatment processes were uneventful. The delays between blood collection and treatment were within the manufacturer's specifications.
- Such occurrences were seldomly reported previously (5 occurrences between 2013 and 2017, none between 2018 and 2020) despite a requirement for bacterial culture upon abnormal PC visual inspection. Underreporting may have occurred.

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Platelet transfusion - related concentrate TTBI near misses

Year	Blood component (pool size)	Shelf life	Bacteria
2013	WBPC (5)	Day 4	*Streptococus.intermedius Staphylococcus.warneri Streptococcus.contellatus*
	APC	Day 4	*Staphylococcus aureus*
2015	WBPC (5)	Day 5	*Staphylococcus aureus*
2017	APC	Day 4	*Citrobacter koseri*
	WBPC (5)	Day 5	*Bacillus cereus*
2021	PR WBPC (8)	Day 6	*Bacillus cereus Staphylococcus epidermidis*
2022	PR APC	Day 7	*Staphylococcus aureus*
2023	PR WBPC (8)*	Day 4	*Bacillus hominis*

Reported TTBI involving PR PC

Year	Country	lity
2015[1]	Switzerlan	e
2016[1]	Belgium	e
2018[2]	USA	
2020[2]	USA	
2021[2]	USA	
2021[2]	USA	?
2021[3]	France	
2023[4]	France	

ACBC: *Acinetobacter ca*
[1] *Benjamin et al, Transfu* *t al,*
ISBT Barcelona, 2024

- **Potential mechanisms for PR failure to prevent TTBI** may involve:
  - resistance to PR
    - spore- and biofilm-forming bacterial species (*Stormer et al, Transf Med, 2008; Schmidt et al, Transfusion, 2015: Cloutier et al, Vox Sanguinis, 2022*)
    - very high bacterial load (*Schmidt et al, Transfusion, 2015*)
    - bacterial pump –mediated amotosalen efflux (*Green et al, mSphere, 2023*)
  - post-PR contamination by means of container leaks (*Fadeyi et al, Transfusion, 2021*) .
- An extended delay between blood donation and amotosalen plus UVA treatment of the BC has been associated with an increased risk of PR failure (*Cloutier et al Vox Sanguinis, 2022*).
- Despite efficient PR, prior bacterial toxin accumulation in the PC could theoretically induce a shock in the recipient (*Chi et al, Vox Sanguinis, 2023*).

Reported TTBI involving PR PC

Year	Country	PC	Bacteria (PC and recipient)	Outcome	Imputability
2015[1]	Switzerland	APC	*Klebsiella pneumonia*	Recovered	Possible
2016[1]	Belgium	WBPC	*Staphylococcus haemolyticus*	Recovered	Probable
2018[2]	USA	APC	*ACBC*	Recovered	Certain
2020[2]	USA	APC	*ACBC* *Staphylococcus saprophyticus* *Leclercia adecarboxylata*	Deceased	Certain
2021[2]	USA	APC	*ACBC* *Staphylococcus saprophyticus* *Leclercia adecarboxylata** *Bacillus spp**	Deceased	Certain
2021[2]	USA	APC	*Enterobacter spp* *Staphylococcus saprophyticus** *Leclercia adecarboxylalata**	Recovered	Certain ?
2021[3]	France	APC	*Bacillus cereus*	Recovered	Certain
2023[4]	France	WBPC	*Bacillus hominis*	Recovered	Certain

ACBC: *Acinetobacter calcoaceticus - baumannii* complex; *: bacteria not identified in the recipient

[1] *Benjamin et al, Transfusion, 2017*; [2] *Kracalik et al, Inf Emerg Dis, 2023*; [3]*Richard et al, Vox Sanguinis, 2023*; [4]*Humbrecht et al, ISBT Barcelona, 2024*

Summary / Conclusions:

- The transfusion of 100% % Intercept™ PR PC resulted in a steep reduction in transfusion-transmitted bacterial infection (TTBI) occurrence in a setting where no bacterial detection was in place.
- TTBI may however still occur. Therefore, careful visual inspection of PC upon issuing, bacterial testing upon suspicion as well as careful patient monitoring during and after transfusion should remain the norm even after the implementation of PR
- PR PC implementation has also provided an additional microbiological safety measure, notably for window-period donations or for PR-sensitive pathogens not tested for.

Zika virus in asymptomatic blood donors in Martinique

Gallian et al, Blood, 2017

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Parvovirus B19 infection in blood donors

- In France, all blood donations undergo Parvovirus B19 NAT testing (for plasma fractionation purposes) on pools of 96 donations with a threshold of 10E4 IU/mL.
- Sharp increase in positive high titer Parvo B19 donations since December 2023
- PR PC mediated Parvovirus infection has been reported (*Gowland et al, Transfusion Med,2016*)

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- PR PC implementation has also provided an additional microbiological safety measure, notably for window-period donations or for PR-sensitive pathogens not tested for.
- Use of Intercept™ PR platelets does not prevent TTI involving non-enveloped virus. Sub-optimal amotosalen concentration inside a tight viral capsid may be contributive.

Acknow

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du Sang

