

Indications and side effects of plasma and plasma products

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Actual use of plasma:

Procedure/clinical indication	Percentage of FFP transfusions
Surgery	33.3%
Warfarin reversal	20.2%
Other coagulopathy	14.3%
Before invasive procedure	5.9%
Bleed	8.4%
Massive transfusion	7.3%
Plasma exchange	3.8%
Trauma	0.3%
Miscellaneous	6.3%

} **>50% acute situations**

Source: Tinmouth, A. et al (2013). Utilization of frozen plasma in Ontario: a province wide audit reveals a high rate of inappropriate transfusions. Transfusion, 53(10), 2222–9.

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Actual use of plasma:

55% of plasma transfusions could be qualified as appropriate based on internationally agreed-upon indications, with fully 28% qualifying as inappropriate and the remainder as indeterminate

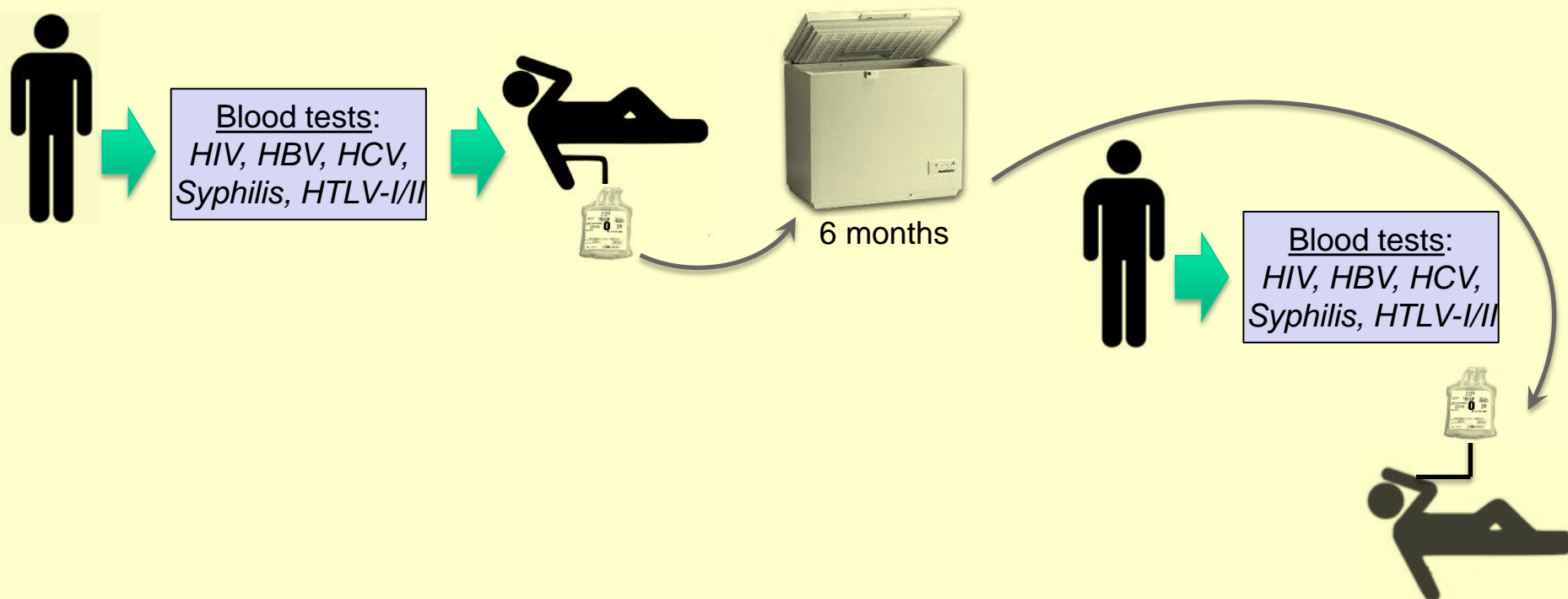
Source: Tinmouth, A. et al (2013). Utilization of frozen plasma in Ontario: a province wide audit reveals a high rate of inappropriate transfusions. Transfusion, 53(10), 2222–9.

Indications and side effects of plasma and plasma products

Available types of plasma:

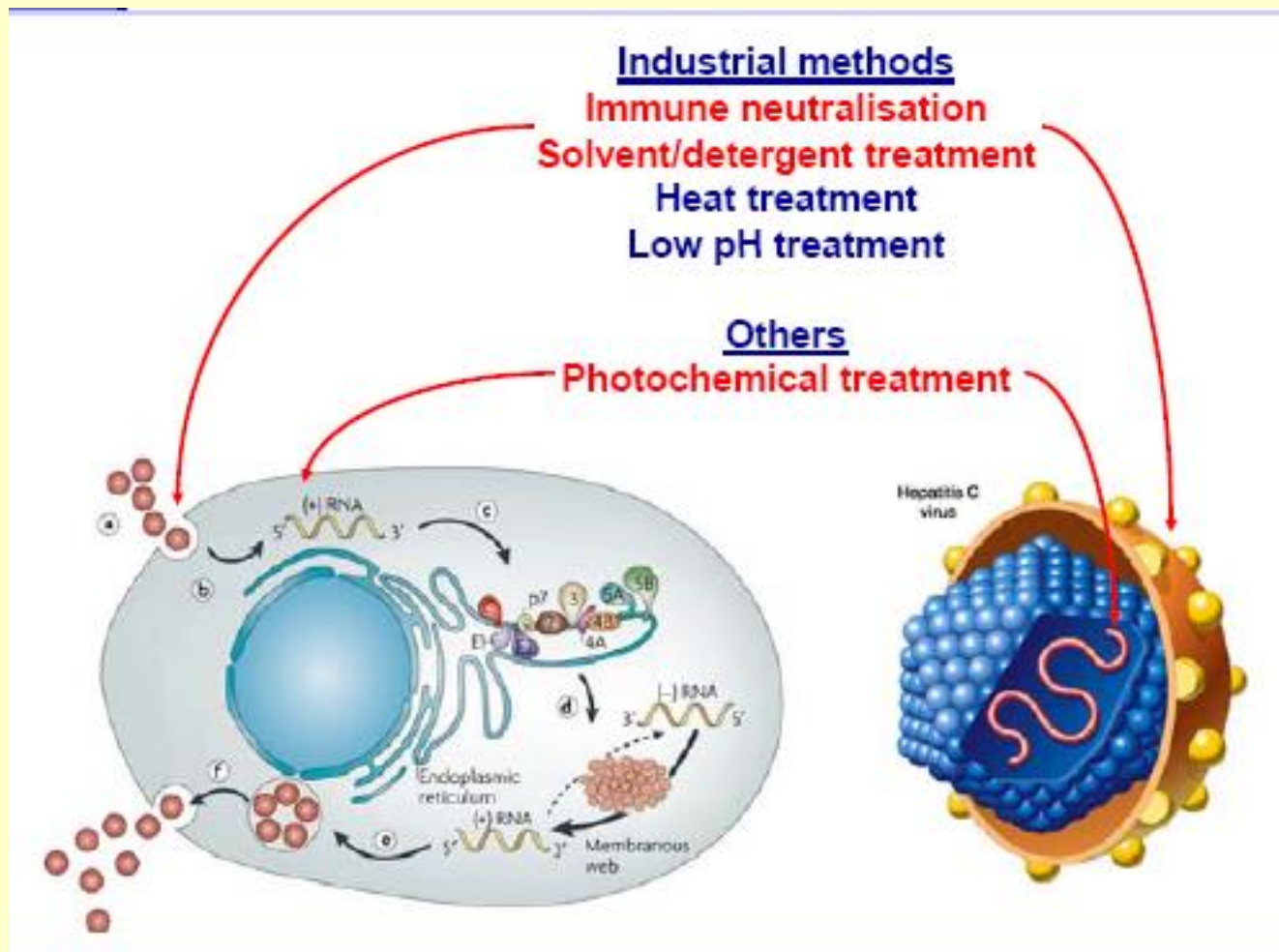
Quarantined Fresh Frozen Plasma (Q-FFP)

- Apheresis plasma (from one donor) stored in quarantine for six months
- Donor tested for certain diseases during donation; retested 6 months later (window period)
- Plasma released for use if donor clears second round of testing & given to patient
- Expiry: 3-36 months after donation (depending on storage temperature)



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Pathogen reduction methods:

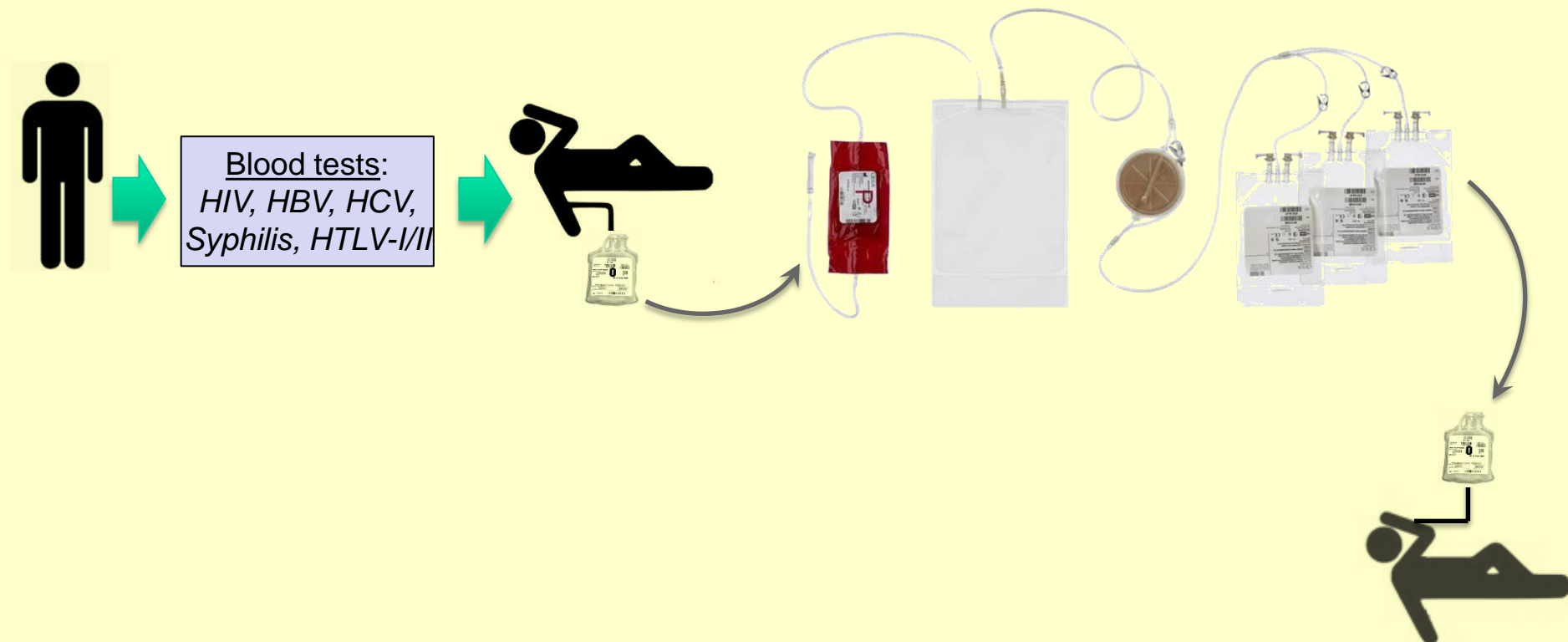


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Available types of plasma:

INTERCEPT Plasma (Amotosalen Inactivated)

- Apheresis plasma (from one donor)
- Units processed using INTERCEPT pathogen reduction system in-house
- Can be used with either freshly collected or frozen plasma which has been recently thawed

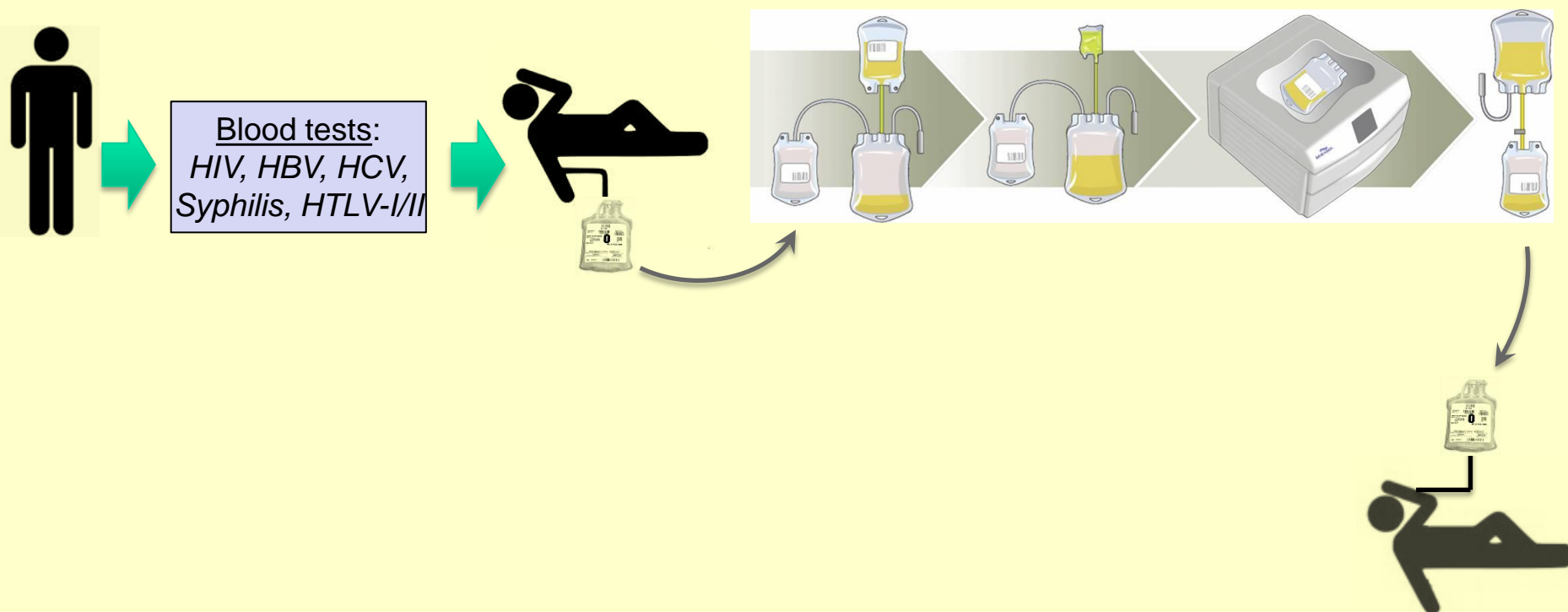


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Available types of plasma:

Mirasol® Plasma (Riboflavin + UV Inactivated)

- Apheresis plasma (from one donor)
- Units processed using Mirasol pathogen reduction system in-house
- Can be used with either freshly collected or frozen plasma which has been recently thawed

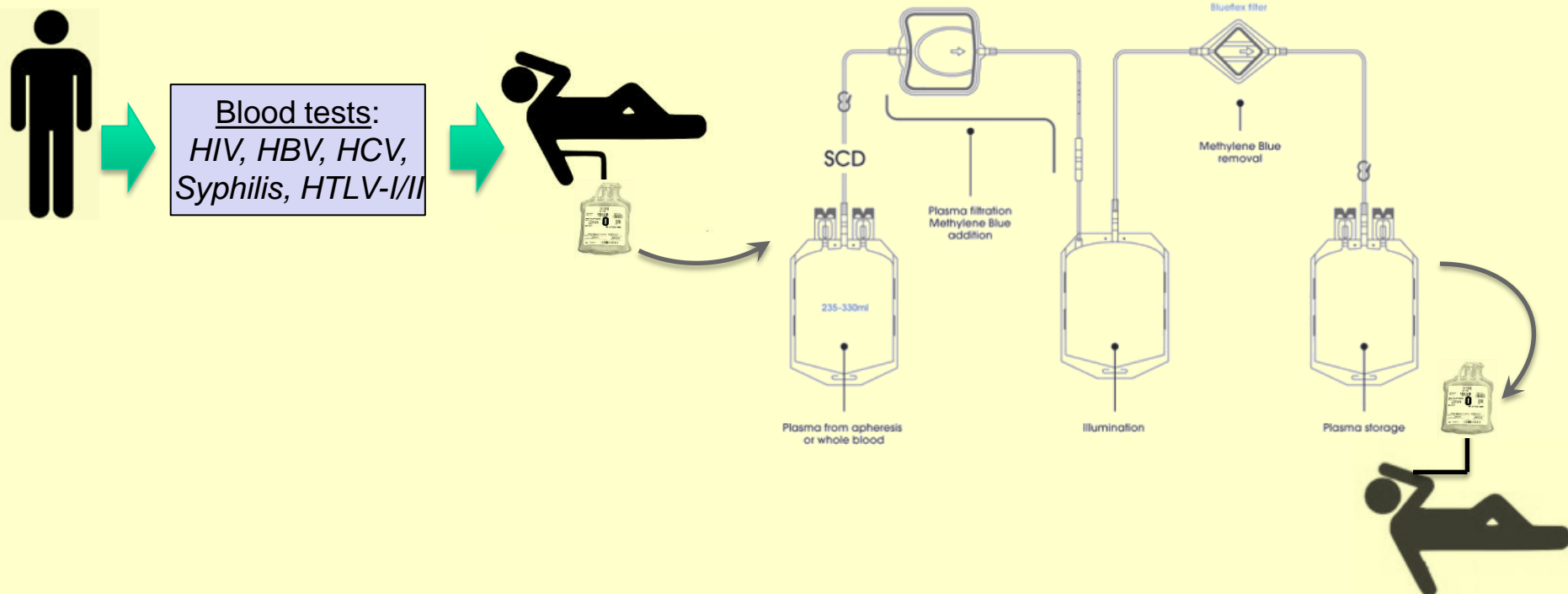


Indications and side effects of plasma and plasma products

Available types of plasma:

THERAFLEX Plasma (Methylene Blue Inactivated)

- Apheresis plasma (from one donor) or whole blood
- Units processed using THERAFLEX pathogen reduction system in-house
- Can be used with either freshly collected or frozen plasma which has been recently thawed

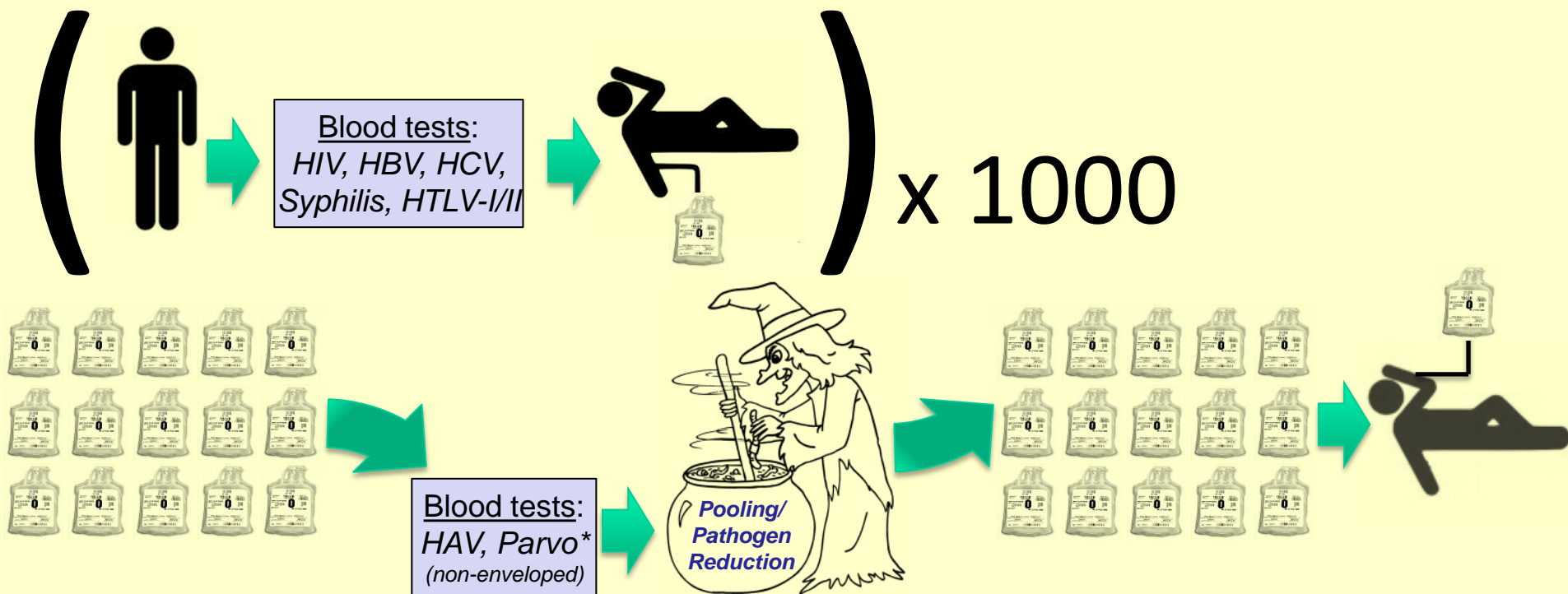


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Available types of plasma:

Solvent/Detergent treated pooled Plasma (SDP) – e.g. Octaplas™, Omniplasma™ (TNBP + Triton X-100)

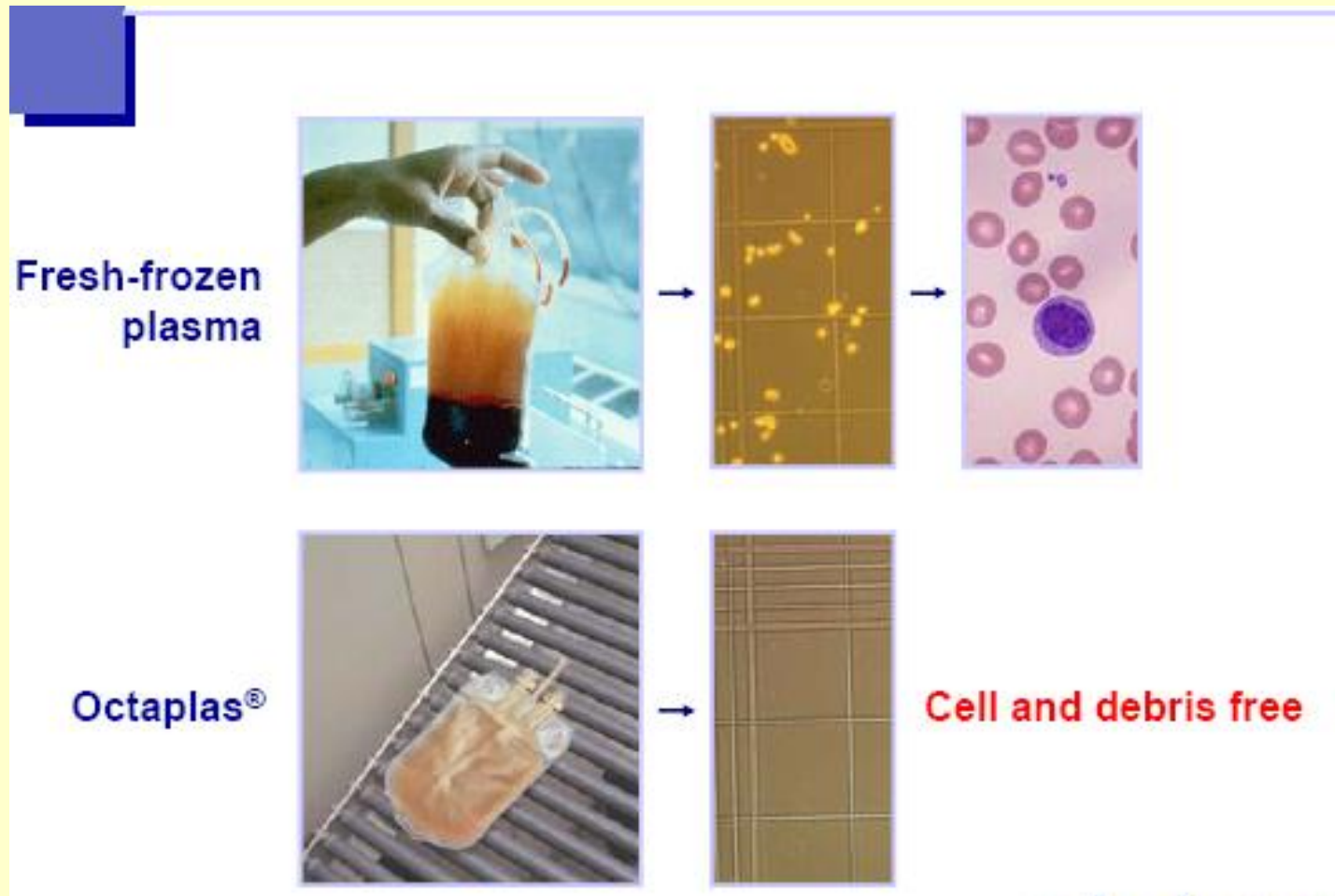
- Plasma from ~1000 donors pooled
- Pool undergoes pathogen inactivation process
- Plasma separated into individual bags of uniform composition



**Test is done to confirm presence of antibodies against these viruses.*

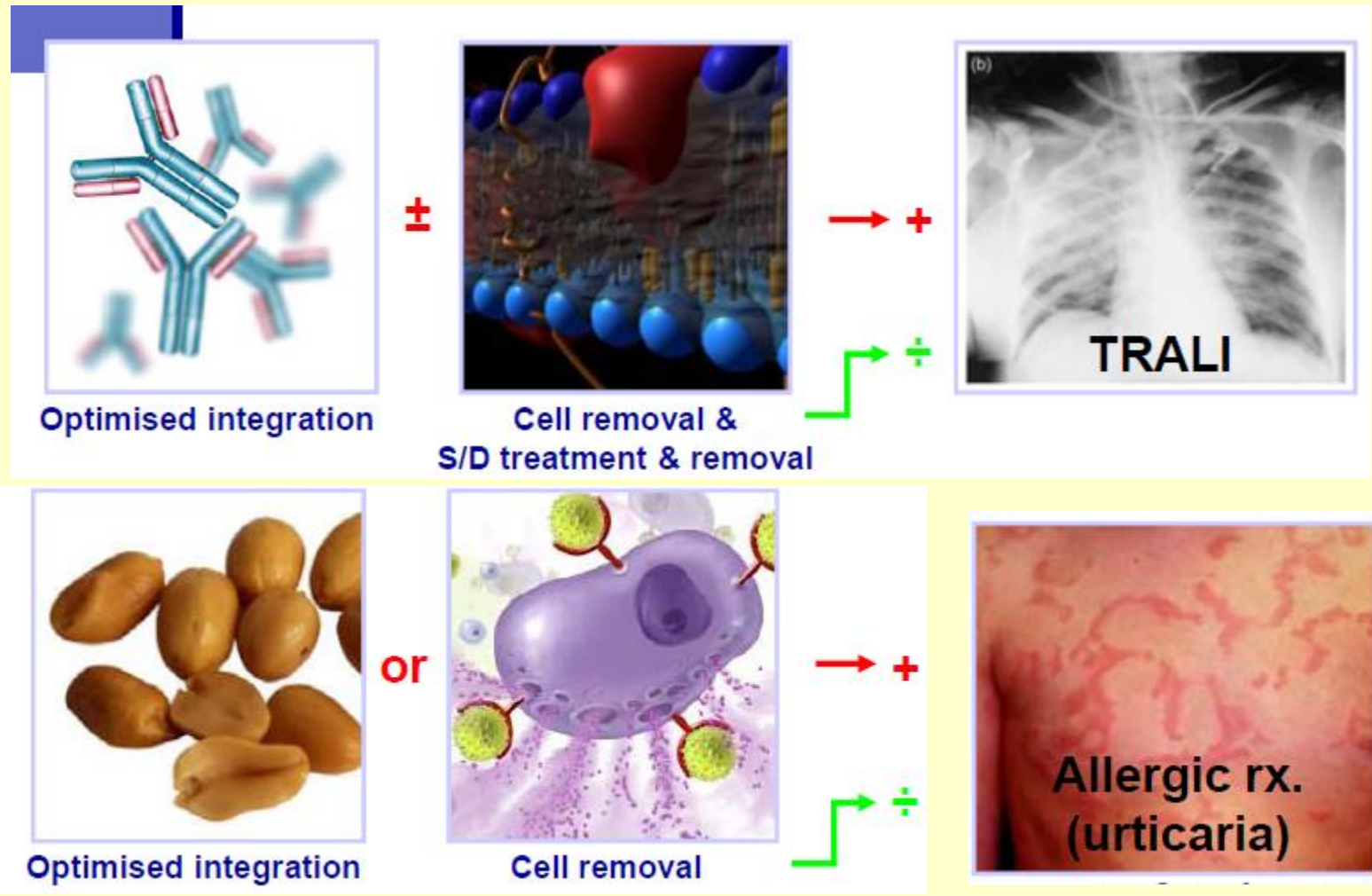
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Effect of filtration:



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Table 1: Usage of various plasma types across European countries

Land (jaarrapport)	Plasmaproduct					Totaal
	Q-FFP	SDP	MB-plasma	Amotosalen	Riboflavine	
Duitsland (2009)	1.066.000	65.000	*	*	*	1.131.000
Frankrijk (2009)	1.400	142.000	205.000	23.000	*	371.400
VK (2009)	307.000	53.000			*	360.000
Nederland (2009)	90.000	*	*	*	*	90.000
België (2006)	*	*	66.000	*	*	66.000
Denemarken (2008)	62.000	*	*	*	*	62.000
Noorwegen (2008)	*	48.000	*	*	*	48.000
Finland (2007)	*	46.000	*	*	*	46.000
Totaal	1.526.400	354.000	271.000	23.000		2.174.400
* niet vermeld in het Jaarrapport						

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Plasma transfusions carry the risk of adverse events, including but not limited to:

- Allergic/Anaphylactic reactions
- Febrile Non-Hemolytic Transfusion Reactions (FNHTRs)
- Hemolytic transfusion reactions (via RBC alloimmunization)
- Septic transfusion reactions
- Transfusion Related Acute Lung Injury (TRALI)
- Transfusion Associated Circulatory Overload (TACO)
- Venous Thromboembolism (both Deep Venous Thrombosis and Pulmonary Embolism)
- Hyperfibrinolysis

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By far the most common reaction. Presents with urticaria and symptoms of general malaise. In rare cases of anaphylaxis, hypotension and stridor present, requiring immediate attention.
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Presents with fever, hypotension and oliguria – requires immediate cessation.
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Presents with fever, hypotension within minutes of transfusion start – requires immediate cessation.
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Presents with bilateral pulmonary edema, dyspnea. #1 cause of plasma transfusion associated mortality
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 - Transfusion Related Acute Lung Injury (TRALI)
Presents with bilateral pulmonary edema, dyspnea. #1 cause of plasma transfusion associated mortality
 - Transfusion Associated Circulatory Overload (TACO)
Presents with hypertension and dyspnea owing to resulting pulmonary edema
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 - Hyperfibrinolysis

The presence of both of these as possible side effects indicates plasma transfusions can lead to both hyper and hypocoagulative states

Indications and side effects of plasma and plasma products

SDP vs. Q-FFP – advantages:

Solvent/Detergent treated pooled Plasma

Consistent plasma protein levels

Fewer allergic/anaphylactic reactions

No Transfusion Related Acute Lung Injury

More effective (smaller volume needed)

Single Donor Plasmas (Quarantined, AI, MB)

Cheaper per mL

Risk of emerging pathogen transmission

Nominal levels of coagulation proteins

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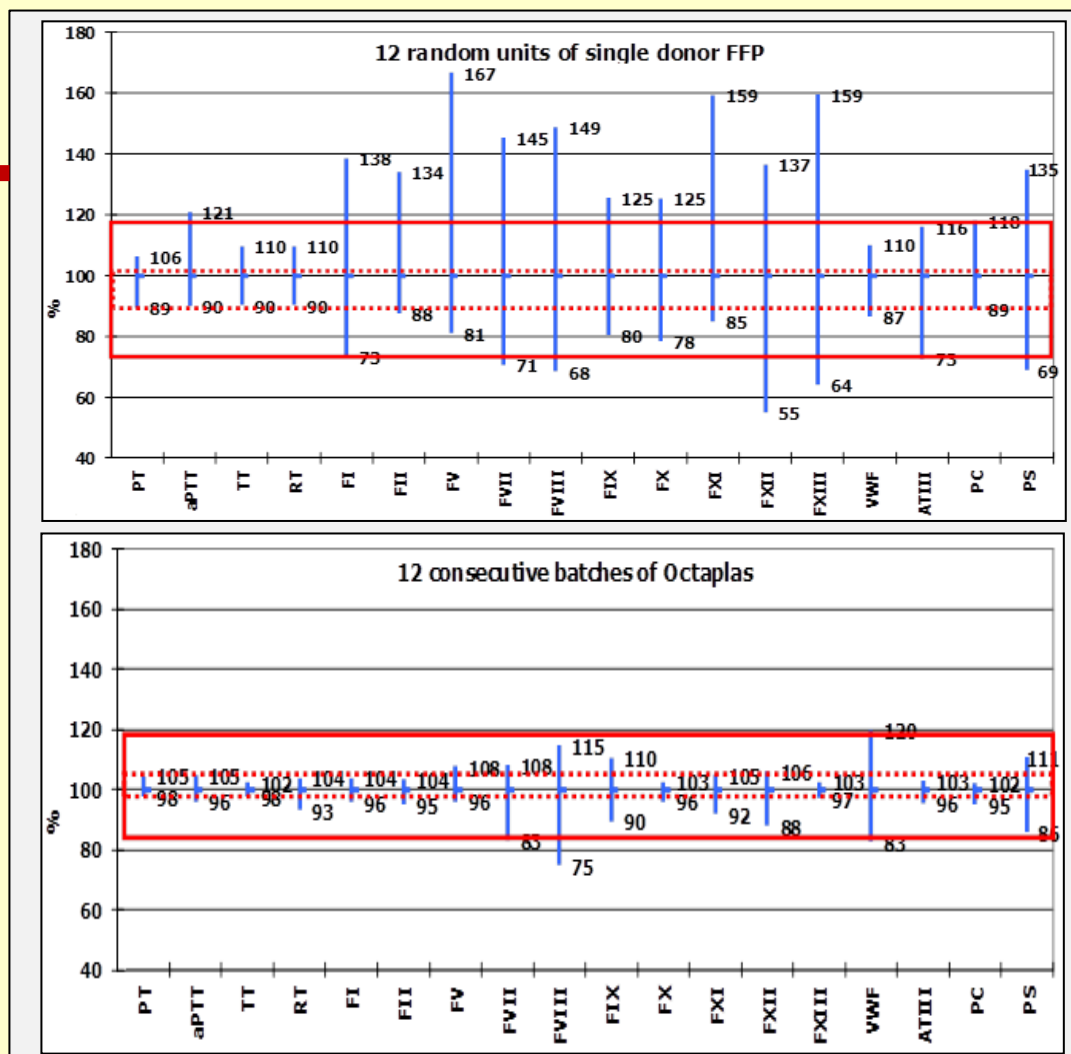
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The rate of allergic/anaphylactic reactions when transfusing SDP is between **76% and 94% lower** than that of FFP*

*Krusius, Tom. "Pooled SD-pathogen inactivated FFP as an alternative to regular FFP", ESTM Course on Appropriate use of plasma products, Zagreb, Croatia. 14-18 November 2012. Conference Presentation.

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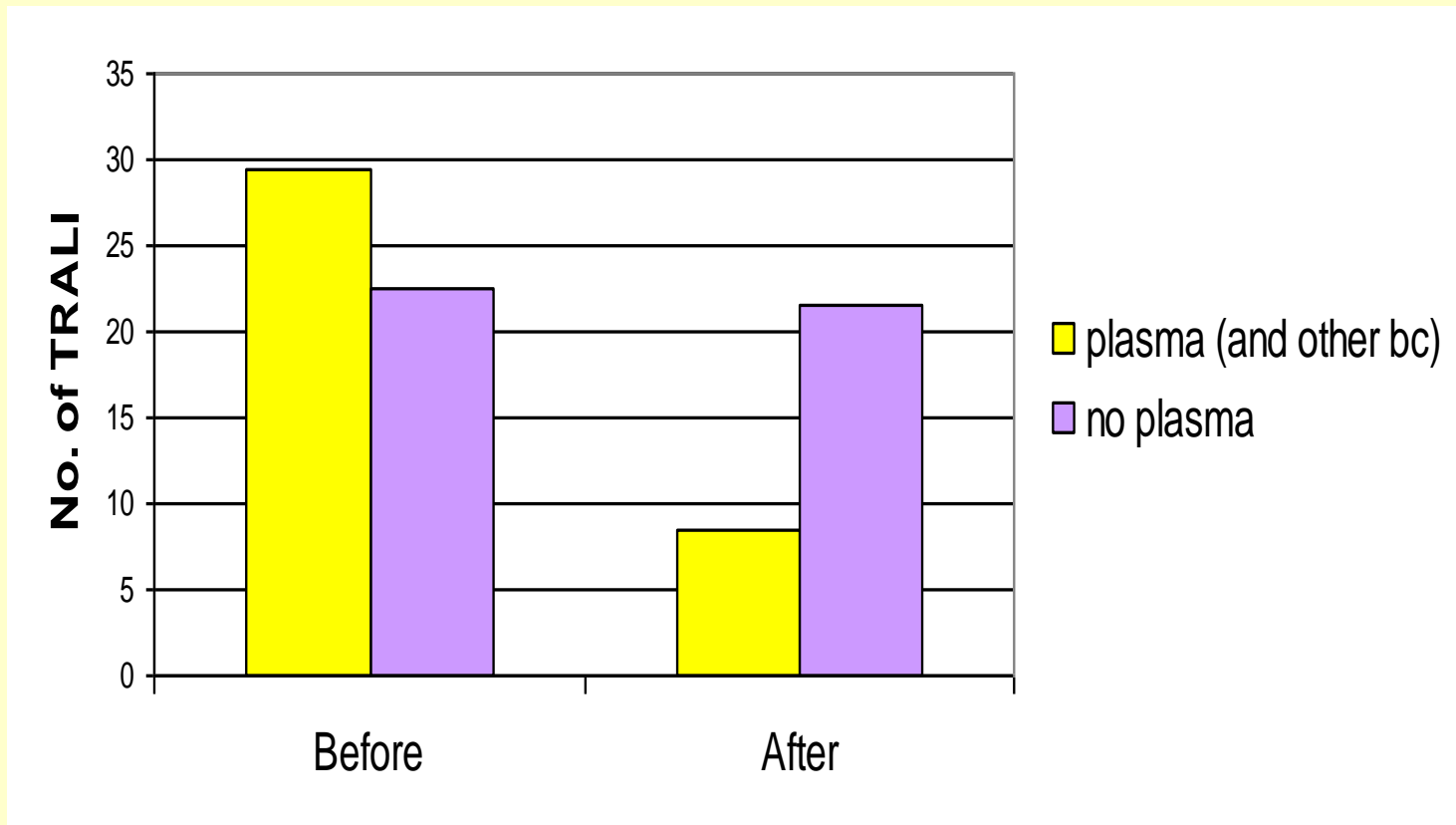
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Nominal levels of coagulation proteins

Since its introduction, there has yet to be a confirmed case of TRALI following SDP transfusion*

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Effect of the male-only measure



PAR: 0.33 (95% CI 0.09 to 0.51)

Excl. “possible TRALI”: 0.37 (0.06 – 0.58)

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Nominal levels of coagulation proteins

Total volume of plasma transfused decreased by 16.2% following replacement of Q-FFP with SDP in Finland (2006-2009 data)*

*Krusius, T., Auvinen, M.-K., & Tuimala, J. (2010). Introduction of Octaplas in clinical use decreased the rate of serious adverse reactions. Vox sanguinis, 99(Suppl. 1), 461..

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Nominal levels of coagulation proteins

Prices vary per country, but SDP tends to be around 25% more expensive by volume.

*Sanquin Bloedvoorziening, 2012, Plasma Assortiment, Sanquin Bloedvoorziening, Amsterdam, the Netherlands.

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SDP has reduced levels of the following plasma proteins:

- Protein S
- α_2 -antiplasmin
- Factor V
- Factor VII

...the lack of Protein S and α_2 -antiplasmin are particularly important as they have been suggested to lead to rather serious side effects:

Low Protein S levels:

VTE during TTP treatment using SDP

Low α_2 -antiplasmin levels:

Hyperfibrinolysis during OLT using SDP

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FDA requests of studies required for final approval of Octaplas:

1. A study to investigate the incidence of hyperfibrinolysis during OLT following use of SDP:
2. A study to investigate the incidence of DVT and PE following repeated SDP transfusions during TTP treatment:

[www.clinical trial.gov](http://www.clinicaltrial.gov) :Not yet recruiting

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Octaplas:

-----WARNINGS AND PRECAUTIONS-----

- Transfusion reactions can occur with AB0 blood group mismatches (5.1) • High infusion rates can induce hypervolemia with consequent pulmonary edema or cardiac failure (5.2)
- **Excessive bleedings due to hyperfibrinolysis can occur due to low levels of alpha2-antiplasmin (5.3)**
- **Thrombosis can occur due to low levels of Protein S (5.4)**
- Citrate toxicity can occur with volumes exceeding one milliliter of Octaplas per kg per minute (5.5)
- Octaplas is made from human blood; therefore, may carry the risk of transmitting infectious agents, e.g., viruses and theoretically, the variant Creutzfeldt-Jakob disease and Creutzfeldt-Jakob disease agent (5.6)

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Incidences of plasma transfusion related adverse events (AEs):

- Reported incidences of most common AEs vary by orders of magnitude
- Reasons for inconsistency of reported incidences include:
 - *Most plasma transfusions take place in acute settings*
 - *Presenting symptoms of most common (allergic) reactions are subtle*
 - *Definitions of FNHTRs vary by country (sometimes even by hospital)*
 - *Pre-medication of patients hampers observation of many common AEs*
- Plasma Transfusion related AEs remain both costly and potentially fatal

Indications and side effects of plasma and plasma products

FROSTED study:

FResh frozen plasma, **O**mniplasma, & **SDP** comparison of **T**ransfusion reactions, **E**fficacy and **DVT** study

- 2-year Dutch study currently in progress
- Goals of study include:
 - *International comparison of AE incidences for various plasma sorts*
 - *Evaluation of Omniplasma™ with regard to AEs, efficacy and DVT*
 - *Estimation of under-diagnosis of plasma transfusion related AEs*

Indications and side effects of plasma and plasma products

With thanks to:

- Tom Krusius, Finnish Red Cross
- Nic Saadeh, Leiden University Medical Center

Questions?