Quarantine of plasma as a mean to reduce the risk of transfusion-transmitted infection: logistics and feasibility A French perspective

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Relevant financial relationship:

I am employed by Etablissement Français du Sang (EFS), the French public transfusion service in charge of collecting and testing blood and plasma donations as well as the issuing of most blood components in France.

Introducing a **quarantine period for plasma up until the donor returns for a subsequent donation with new set of testing for infectious markers:**

- If the results for the infectious markers are negative, the plasma produced from the previous donation can then be released.
- If the donor does not return by the end of the quarantine period, the units is not released, but can possibly be repurposed for additional manufacturing including pathogen reduction steps

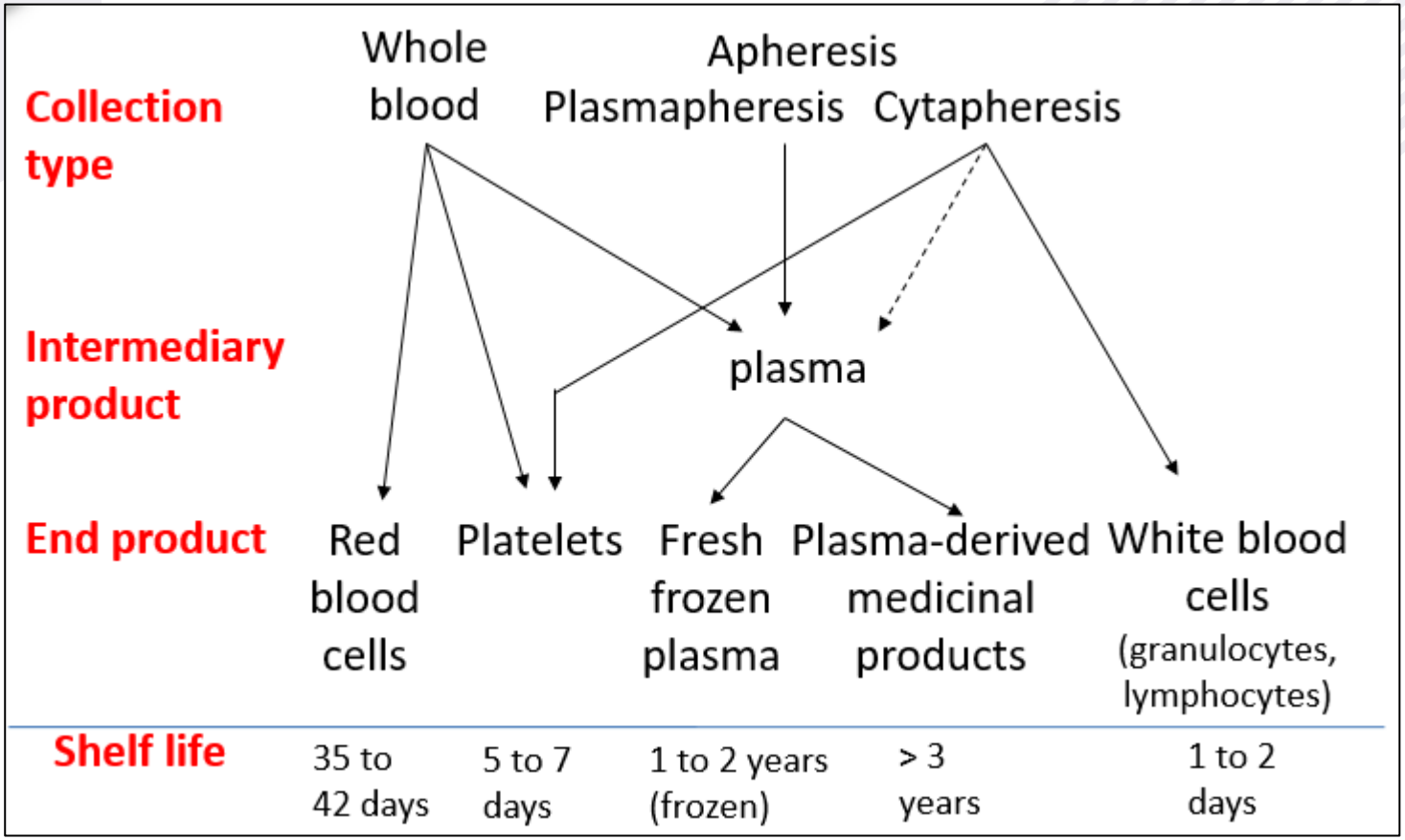
Such a system **contributes to avoiding the risks of transfusing plasma from a donation that was collected previously in a window period of infection**

Prevention of transfusion-transmitted infections

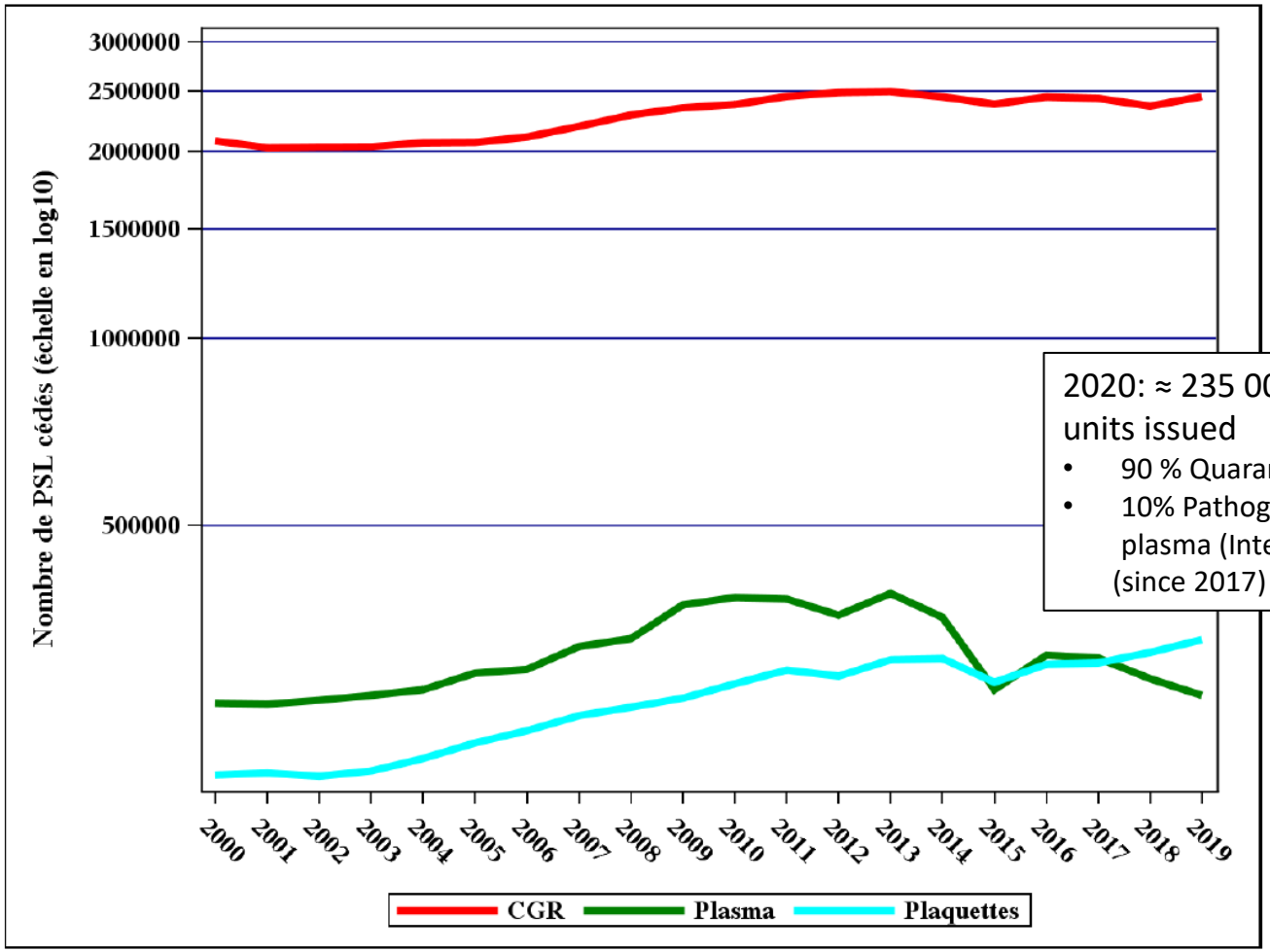
- Donor selection
- Post-donation information
- Donor testing:
  - Serology / Ag screening
  - Nucleic acid testing
- Product leucodepletion
- Pathogen reduction (platelets, plasma, PDMPs manufacturing steps)
- **Product quarantine, pending donor testing on a subsequent donation**

Limitations:

- Inadequate donor information or compliance
- **Donation during a serology or nucleic acid testing (NAT) window period**
- Testing errors: pre (donor misidentification, …), per and post analytic errors
- Resistance to pathogen reduction technologies: non-enveloped virus (Hepatitis E virus, Parvovirus B19, …), high pathogen load
- Manufacturing malfunctions


Collection type
Whole blood
Apheresis
Plasmapheresis
Cytapheresis
Intermediary product
plasma
End product
Red blood cells
Platelets
Fresh frozen plasma
Plasma-derived medicinal products
White blood cells (granulocytes, lymphocytes)
Shelf life
35 to 42 days
5 to 7 days
1 to 2 years (frozen)
> 3 years
1 to 2 days

Plasma issuing in France



2020: ≈ 235 000 plasma units issued

- 90 % Quarantine plasma
- 10% Pathogen-reduced plasma (Intercept™) (since 2017)

* Source : CRH-ST, EFS, CTSA

Quarantine plasma in France

- Quarantine plasma (QP) for transfusion (not for fractionation)
- Plasma from apheresis or whole blood donation (with negative infectious markers)
- **> 60 days quarantine**, frozen plasma (quick freezing within 24 hours after collection, maintained < - 25 degrees C, electric freezers)
  - ✓ Subsequent donation before day 61:
    - Negative for infectious markers: QP is maintained in quarantine
    - Positive for infectious markers: QP is destroyed
  - ✓ Subsequent donation between day 61 and day 160 :
    - Negative for infectious markers: QP is made available for transfusion
    - Positive for an infectious marker: QP is destroyed
  - ✓ No subsequent donation between day 61 and day 160 : QP oriented towards fractionation

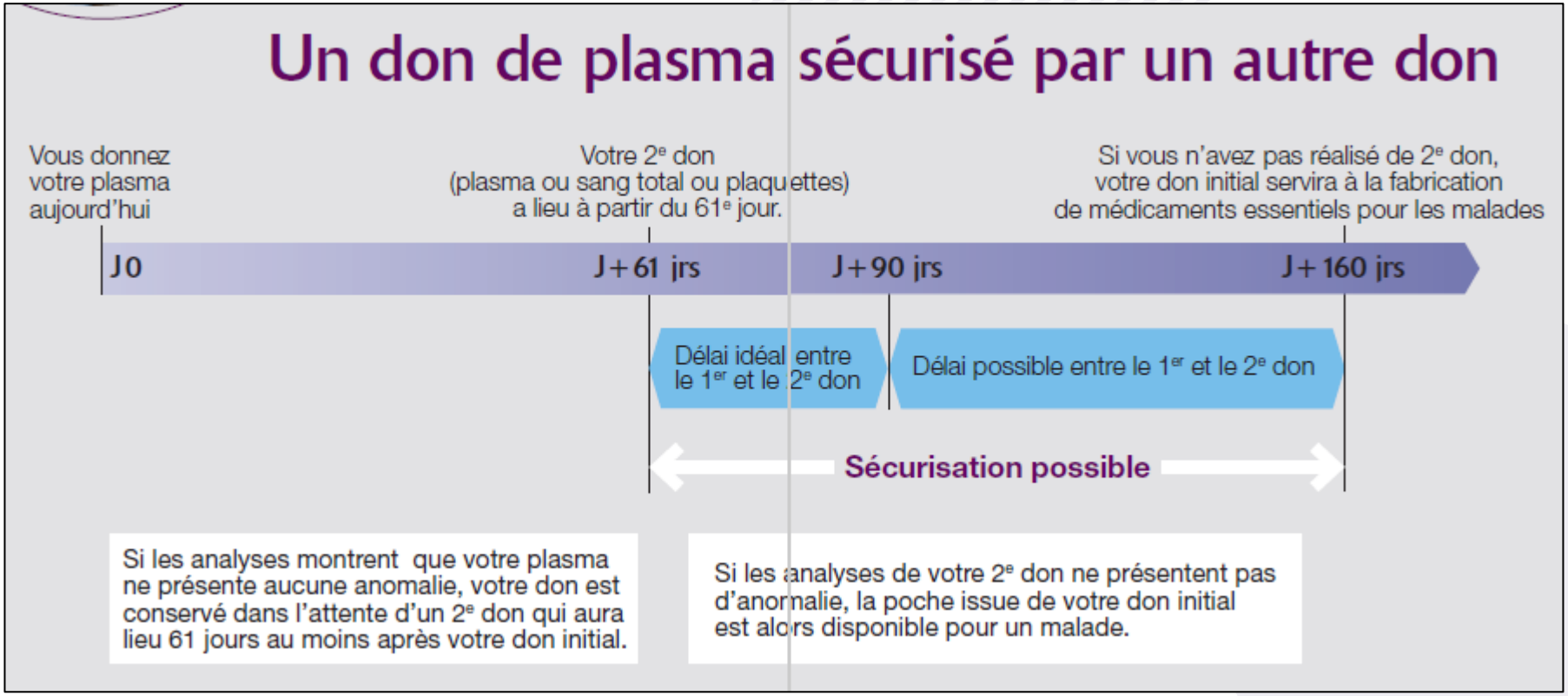
Donation frequency:

- Whole blood donation: up to 6 / year (men) and 4 / year (women)
- Plasma apheresis: up to 24 / year
- Combined plasma / platelet apheresis: up to 12 / year

Infectious markers:

- Mandatory: HIV*, HCV*, HBV*, HTLV-1/2 (new donor), syphilis (*Ab screening and NAT)
- Optional: Any other pathogen screened at both donations (HAV, HEV, malaria, West Nile Virus,…) (per epidemiological status)

“A plasma donation secured by another donation”

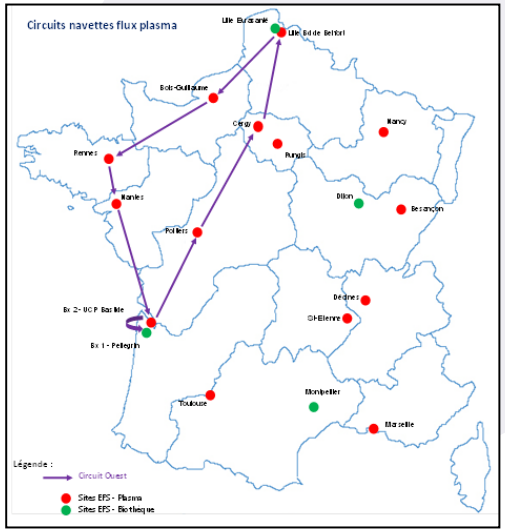


Minimal quarantine period: a function of the window period for the relevant pathogens
Maximum quarantine period: a function of plasma destination (plasma shelf-life, production and logistics considerations ,…)

Quarantine plasma, France

- In 2020, ≈ 212 000 issued quarantined plasma units
- 87 % whole blood donation plasma, 13% apheresis plasma (from B and AB blood groups donors mainly)
- Successful quarantine rate (i.e. q new donation between day 61 and day 160): 45% whole blood donation plasma, 65% apheresis plasma
  - Variable from one regional blood establishment (BE) to another within EFS: highly dependent on the ability to identify and win the loyalty of repeat donors
  - Relying on permanent collection sites or mobile sites (whole blood) with blood collections at least 4 / year
- The number of plasma entered in the quarantine program is dependent on the successful quarantine rate: approximately twice the needed number of QP are subject to a quarantine
- Quarantined plasma are maintained in the local BE for 5 weeks, then transferred to the national quarantine plasma bank (in Bordeaux) for the remaining quarantine period and for subsequent dispatching (plasma for transfusion or plasma for fractionation depending on the post-quarantine status)

QP logistics (example)



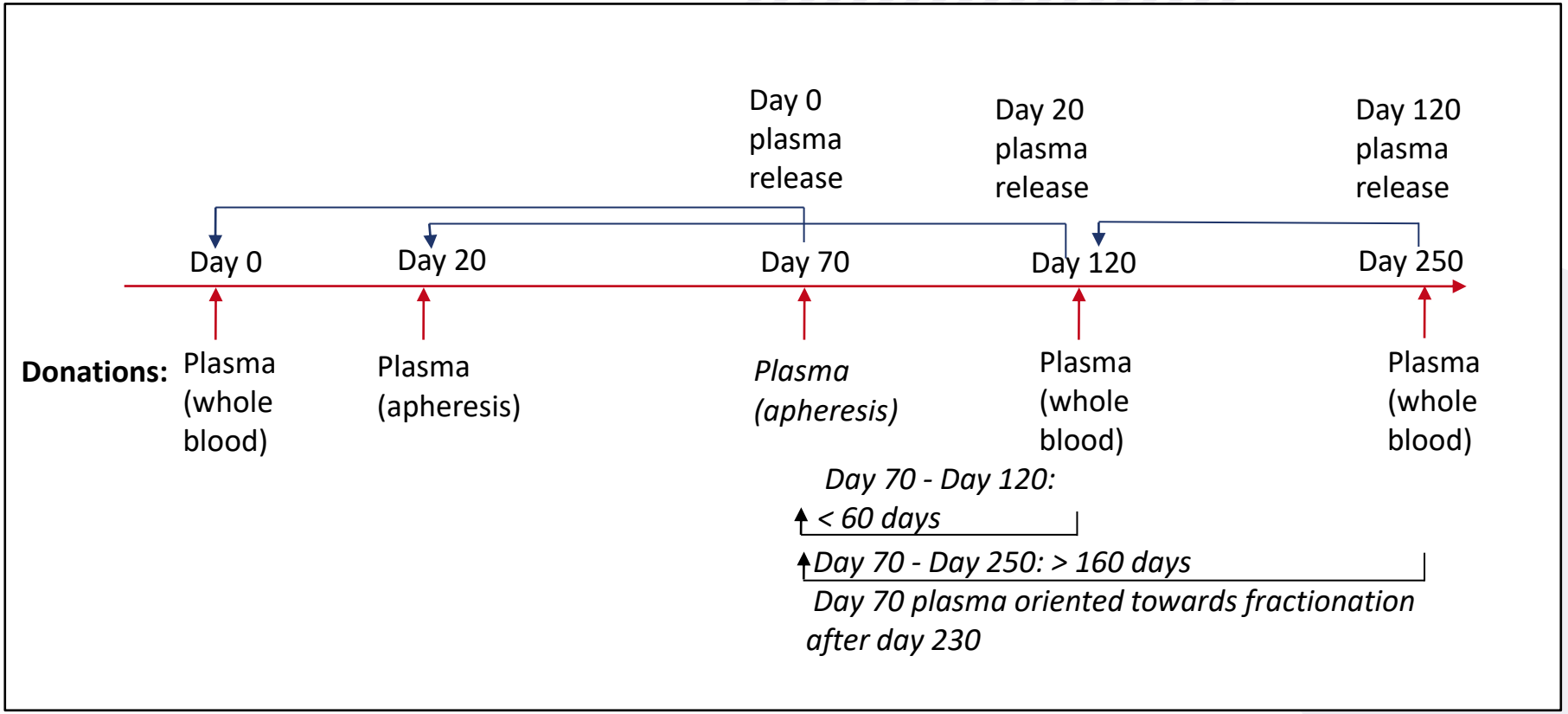
Quarantine plasma, France

- Rigorous product information and traceability:
  - Product code (plasma for fractionation from whole blood / apheresis) and blood group
  - Donor code (linked information include name, gender, address, date of birth, location of birth, blood group, donation history)
  - Donation code (linked information include date, location, plasma volume)
- All manufacturing steps under one integrated nationwide IT infrastructure
- Secure facilities with robust freezing and monitoring capacities

- To be quarantined: the plasma has to clear all (infectious and non-infectious) qualification steps.
- To be issued: a subsequent donation (with or without quarantine plasma) between day + 61 and day + 160 has to clear all infectious qualification steps.

Quarantine plasma, France

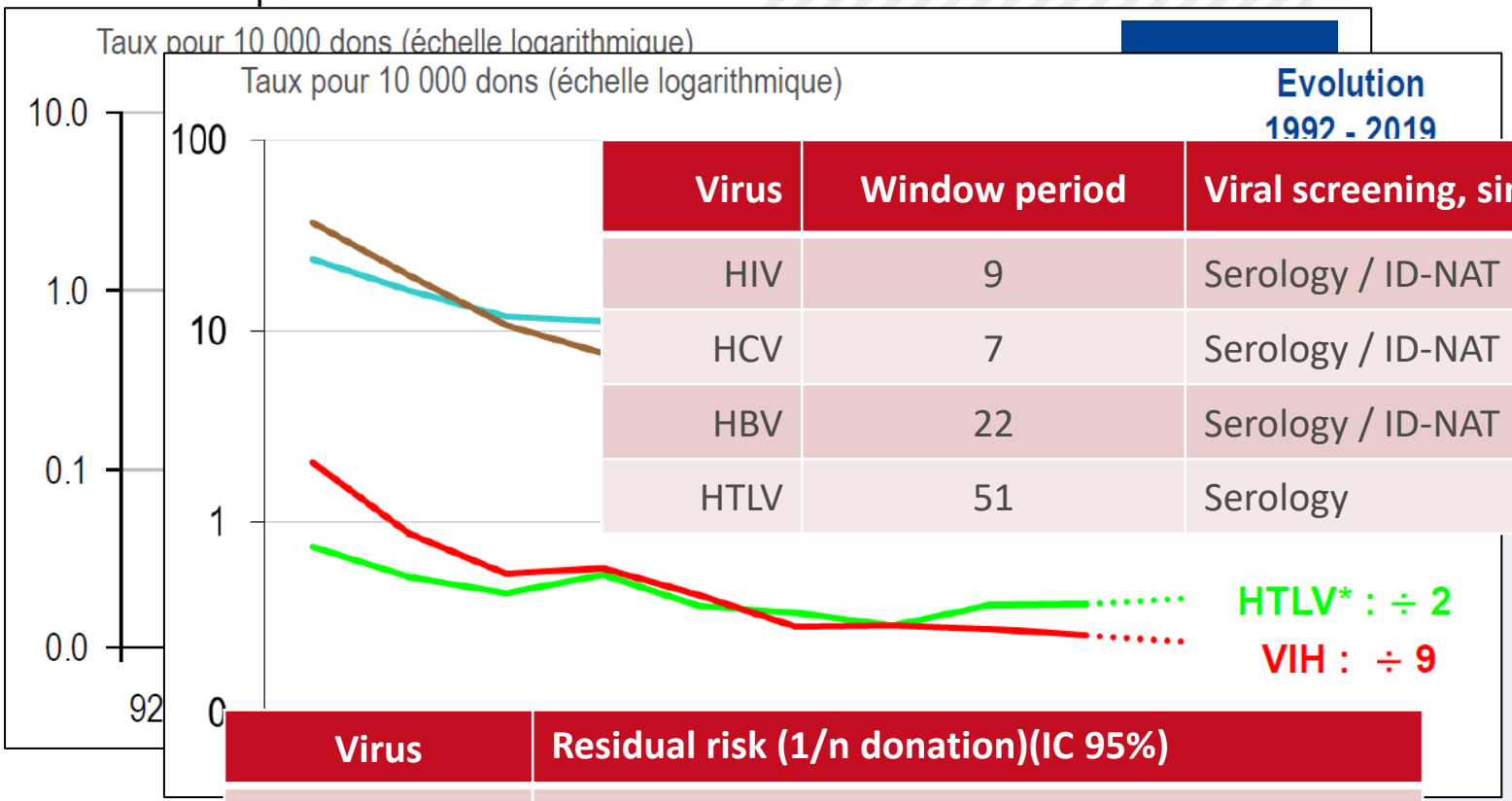
An hypothetical example of a frequent quarantine plasma donor



Donations may occur anywhere in France, possibly in different sites

Estimated transfusion-transmitted infections residual risk, France
A risk that may be prevented by the quarantine process

Incidence and prevalence of transfusion-transmissible infections



Virus	Window period	Viral screening, since 2010
HIV	9	Serology / ID-NAT
HCV	7	Serology / ID-NAT
HBV	22	Serology / ID-NAT
HTLV	51	Serology

Virus	Residual risk (1/n donation)(IC 95%)
HIV	1 / 9 000 000 (0 - 1 / 1 750 000)
HCV	1 / 23 000 000 (0 - 1 / 2 000 000)
HBV	1 / 3 700 000 (0 – 1 /1 300 000)

Quarantine plasma in France
Infectious markers in the subsequent donation

January 2016 to April 2020 (4 years and 3 months)

- 2 566 815 (negative) donations subjected to plasma quarantine

- 45 (<0,002%) donations for which a subsequent donation was found positive (HIV, HBV, HCV, HTLV, Syphilis) (1 donation with 2 markers) :
  - 4 HIV (36, 225, 251, 254 days after initial donation)
  - 4 HBV (112, 277, 344 and 720 days) (+ 5 HBc)
  - 4 HCV (181, 609, 735 and 931 days)
  - 1 HTLV (86 days)
  - 28 Syphilis (mean: 534, s.d. 325)

- For HIV, HBV, or HCV positive subsequent donations, and when possible (previous donation less than 3 years, 10/13, 76%), an archived plasma sample of the initial donation was retested (look-back): confirmed negative in all cases

- In one recent case involving a donation without quarantined plasma, a similar look-back after an HIV positive donation was found positive with a very low unquantifiable HIV viral load when tested with an alternative NAT technology (Cappy et al; Transfusion, 2020)

Estimated residual infectious risk before plasma quarantine
Impact of quarantine as a function of local infection epidemiology and testing performances

- The estimated residual risk before quarantine for quarantined plasma is similar to the estimated residual risk for all blood products
- This estimated residual risk is highly dependent on a number of variables, among which the performance of screening tests (which determines the window period duration) and local incidence of relevant pathogens

Virus	Estimated residual risk (1/n donation) (IC 85%) before quarantine in France
HIV	1 / 7 100 000
HCV	1 / 38 000 000
HBV	1 / 4 400 000

Theoretical estimate:
Impact of an increased number of positive subsequent donations (x 25) and/or increased window period (x 3) on the HIV residual risk

Window period (days)	*Positive subsequent donation (n)*	*Estimated residual risk before quarantine (1/n)*	*Fold increase of the residual risk before quarantine*
9	*4*	*1 / 7 100 000*	*Ref*
9	*(x 25) = 100*	*1 / 574 981*	*≈ 10*
(x 3) = 27	*4*	*1 / 2 577 049*	*≈ 2,4*
(x 3) = 27	*(x 25) =100*	*1/ 245 986*	*≈ 25*

Conclusion :

- Plasma quarantine will mitigate the infectious risk associated with a whole blood / plasma donation occurring during an infectious window period.
- Overall efficiency of plasma quarantine will depend on:
  - The ability to identify and engage with donors who will undergo a timely repeat donation
  - The availability of a robust infrastructure capable of dealing with a large inventory of frozen plasma undergoing quarantine
  - The sensitivity of screening tests and resultant length of infectious window periods
  - The incidence rate of transfusion-relevant pathogens in donors
  - The destination of plasma for which successful quarantine is unconfirmed (absence of a timely subsequent donation).
- Cost-utility studies assessing the impact of these different variables are lacking.
- In countries with a very low estimated transfusion transmitted infections residual risk, plasma quarantine will only marginally increase infectious safety.

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