



INSTITUT NATIONAL DE LA TRANSFUSION SANGUINE

Thierry PEYRARD

PharmD, PhD, EurClinChem

**National Immunohematology Reference Laboratory
(CNRGS)**

Rare donors: The French experience

***BBTS 30th Annual Conference
Harrogate – UK***



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Rare blood: The French experience

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RARE DONORS/PATIENTS

- Any donor may become a patient and vice-versa
- For antigens not routinely tested, rare donors are usually found out at the time they were alloimmunized patients
- Recruitment of rare donors makes sense only if patients with a rare type exist and need blood!

**WHAT IS A RARE
BLOOD TYPE IN FRANCE?**

ARRETE

Arrêté du 28 décembre 1995 relatif aux conditions d'utilisation de prélèvements de sang ou de composants du sang correspondant à des groupes sanguins érythrocytaires rares, pris pour l'application de l'article D. 666-4-2 du code de la santé publique

NOR: TASP9620015A

Le ministre du travail et des affaires sociales,

Vu le code de la santé publique, et notamment ses articles L. 666-4 et D.

666-4-2,

Arrête :

Art. 1er. - Peut être utilisé pour préparer des produits sanguins labiles à usage thérapeutique direct, sous réserve que les conditions prévues ci-après soient respectées, un prélèvement de sang ou de composants du sang sur lequel n'ont pas été effectués tous les tests mentionnés au 5o du I de l'article D. 666-4-2 du code de la santé publique, ou pour lesquels les résultats de ces tests ne sont pas connus ou ne sont pas tous négatifs, à l'exception des tests de détection des anticorps anti-V.I.H.-1 et anti-V.I.H.-2, qui doivent toujours être effectués et dont le résultat doit être négatif :

1. Le prélèvement de sang ou de composants du sang doit présenter un groupe sanguin caractérisé par l'absence d'un antigène de fréquence élevée dans la population dès lors que la fréquence du groupe sanguin ainsi caractérisé est inférieure à 4 p. 1 000 ;

Legal definition (1996): < 4/1,000

LEGAL DEFINITION IN FRANCE

Prevalence < 4/1,000 (i.e. <1/250)

Why such a value?

Defined in the early 90s by:

- Pr Luigi Luca Cavalli-Sforza (University of Stanford)
- Pr Jacques Ruffier (Collège de France - Paris)
- Pr Philippe Rouger (University Curie - Paris)

Adopted from the 2 most frequent genetic diseases in Europe (~1/250):

- Coeliac disease
- Hemochromatosis type 1

DEFINITION OF RARITY

Controversial and heterogeneous!

1/250 in France

1/200 at the New York Blood Center

1/1,000 AABB standards “unusual group”

1/5,000 AABB standards “rare group”

1/10,000 AABB standards “very rare group”

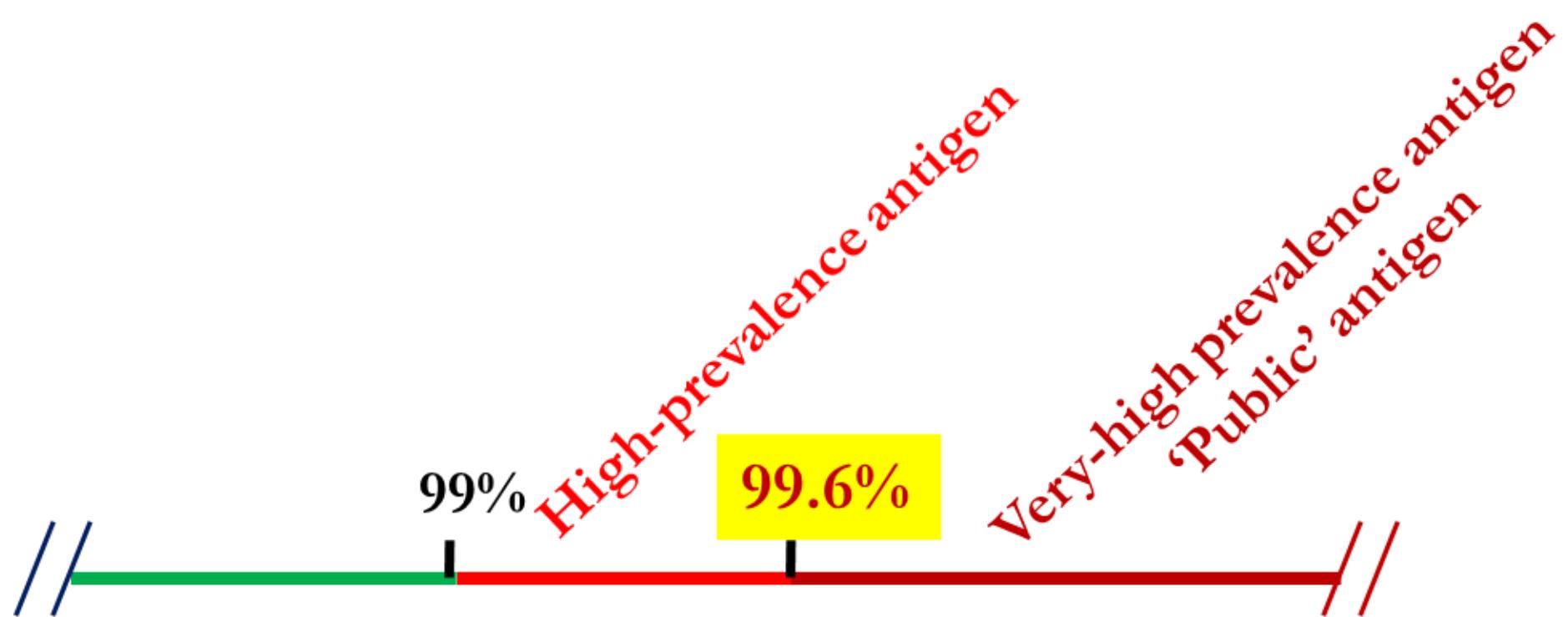
Usual consensus value: <1/1,000

Reesink HW & al. Donors with a rare pheno (geno) type. Vox Sang 2008

THREE BACKGROUNDS

- **Absence of a high-prevalence antigen in the general population**
- **Absence of several common antigens within the same blood group system**
- **Absence of multiple common antigens in the general population, within several blood group systems**

ABSENCE OF A HIGH-PREVALENCE ANTIGEN



Definition of a public Ag in France:
prevalence > 99.6%

ABSENCE OF SEVERAL COMMON ANTIGENS WITHIN THE SAME BLOOD GROUP SYSTEM

| | | | Literature | France* |
|-------------------------------|------------|-------|------------|-------------------|
| r'r' | D-C+E-c-e+ | dCCee | 4/10,000 | 7/100,000 |
| r"r" | D-C-E+c+e- | dcCEE | 1/10,000 | 3/100,000 |
| R _Z R _Z | D+C+E+c-e- | DCCEE | 1/10,000 | 1/100,000 |
| r _y r _y | D-C+E+c-e- | dCCEE | < 1/10,000 | 3/10 ⁷ |
| r _y r' | D-C+E+c-e+ | dCCEe | < 1/10,000 | |
| r _y r" | D-C+E+c+e- | dCcEE | < 1/10,000 | |

* Peyrard T. & al, Vox Sang 2010 (Suppl ISBT Berlin)

ABSENCE OF MULTIPLE COMMON ANTIGENS WITHIN SEVERAL BLOOD GROUP SYSTEMS

- “Rare type combination” or “multiple negative common antigens” type
- Example:

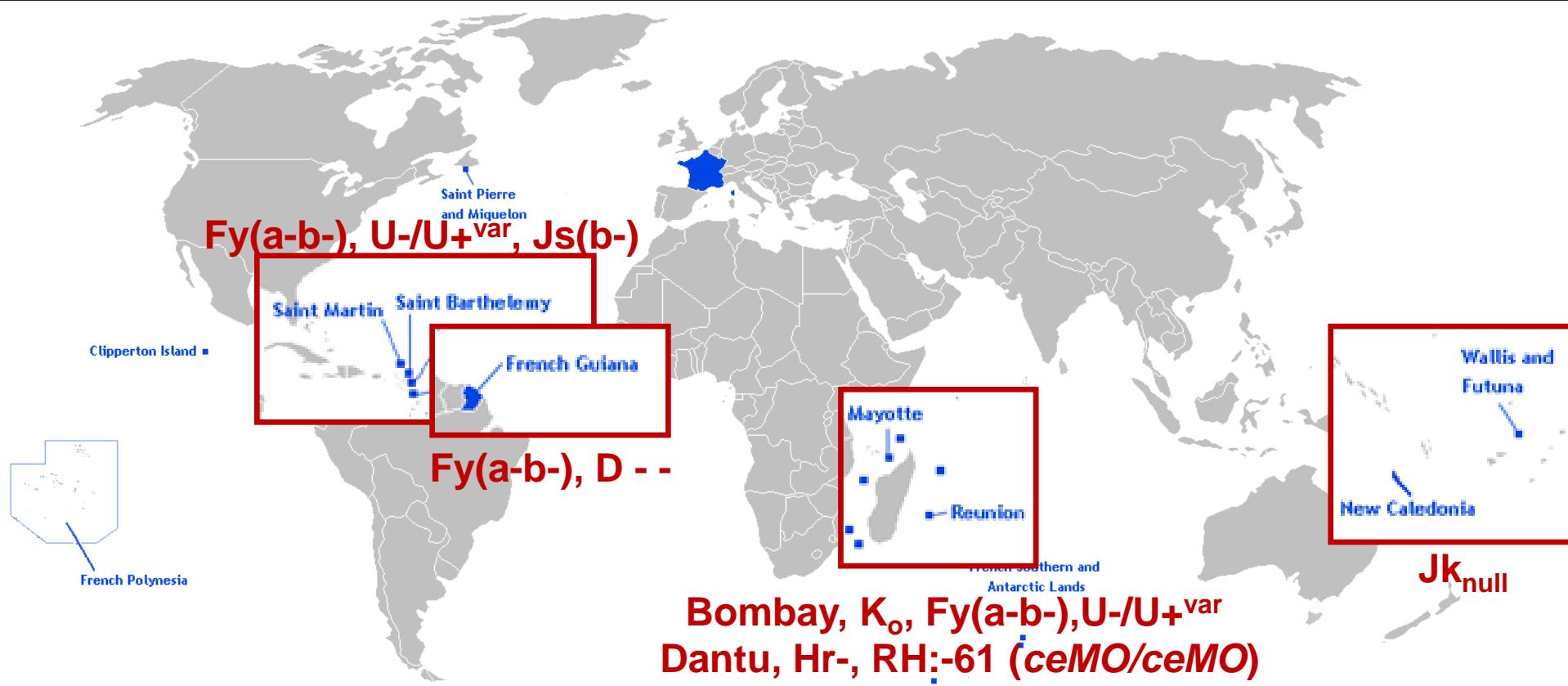
O, D⁺C-E⁺c⁻e⁻, K⁻, Fy(b⁻), Jk(b⁻), s⁻ patient with anti-e, anti-K, anti-Fy^b, anti-Jk^b and anti-s
- Not considered anymore to be a rare blood type in France: works since 2008 on a national solidarity basis (10-15% of repeat donors are typed for FY/JK/MNS)

EPIDEMIOLOGICAL DATA IN FRANCE

POPULATION BACKGROUND

- France: 65 million inhabitants
- Ethnically mixed population
 - Overseas territories
 - Migrant people from former French colonies of Africa

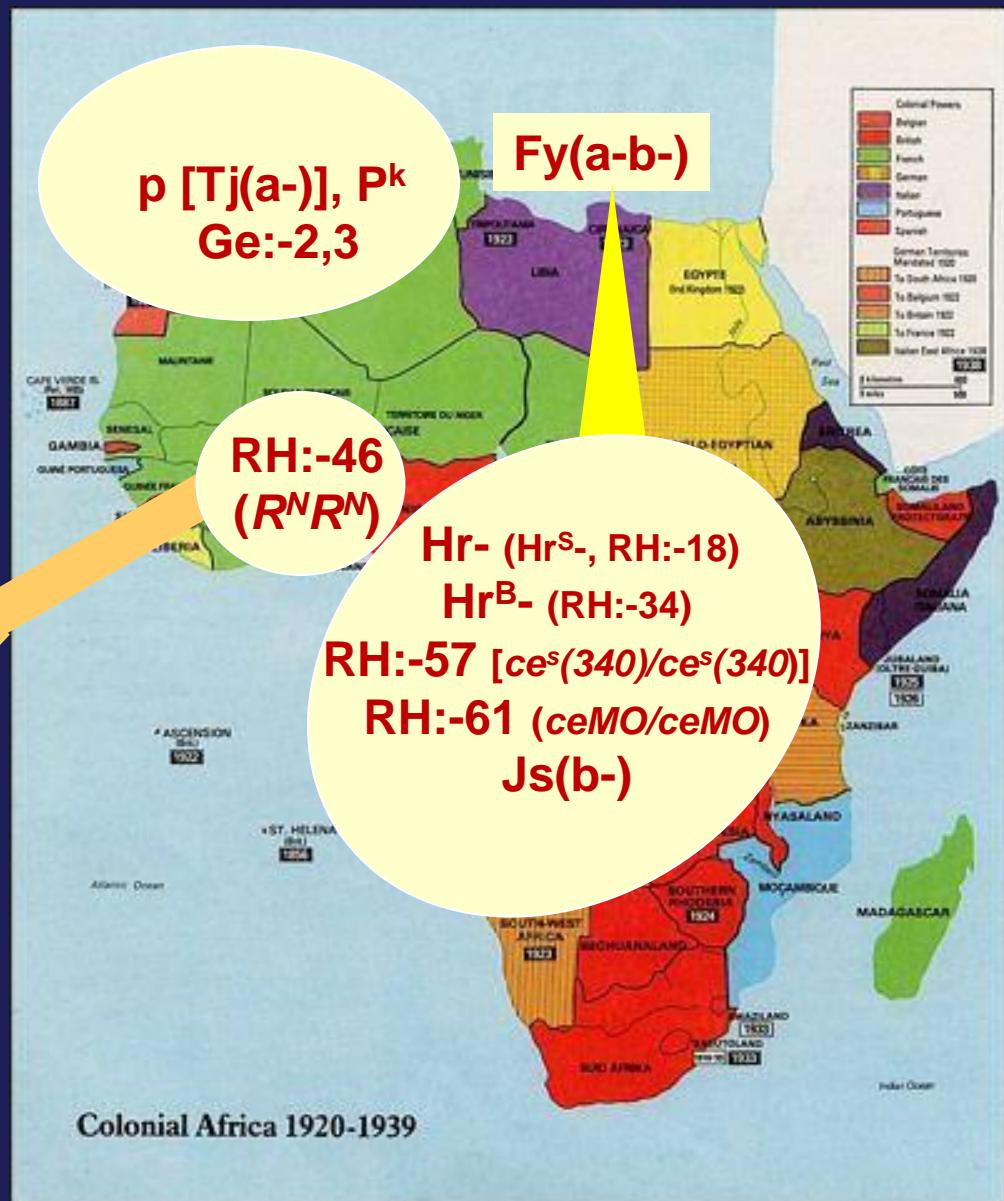
POPULATION BACKGROUND



French overseas territories

POPULATION BACKGROUND

Former French colonies of Africa



NUMBER OF PEOPLE IN FRANCE WITH A RARE BLOOD TYPE

If we consider the 9 most prevalent rare blood specificities in the French **Caucasian population (61.10^6 inhab.)**:

- k-, Yt(a-), Lu(b-), Co(a-): $4 \times 125,000$
- r'r', Vel- and Kp(b-): $3 \times 25,000$
- Ge:-2: 12,000
- r''r'': 6,000

=> ~ 600,000 people

NUMBER OF PEOPLE WITH A RARE BLOOD TYPE

People of African ancestry within the official immigrant population:

- Fy(a-b-), C-E-, K-, Jk(b-), S-, VS-, Js(a-):
~ 100,000
- U- and U+^{var}: ~ 10,000
- Js(b-), Hr-, Hr^B-, RH:-46, RH:-57, RH:-61, etc:
~ 30,000

These data estimation do not include the French Antilles, nor people of African ancestry who were born in France

Total of ~ 750,000 people with a rare type in France (>1% of the population)

POPULATION BACKGROUND

- Number of people of African descent supposed to be over 4 million
- 12,000 patients with sickle cell disease (> 15,000 with overseas territories). Top 1st genetic disease
- Number of SCD patients expected to rise up to 30,000 by the next 10 years
- Low ratio of donors of African descent

NATIONAL REGISTRY OF PEOPLE WITH A RARE BLOOD TYPE

- National Registry created in the 60s
- France is one of the only country in the world which enlists **both patients and donors** with a rare blood type in a **unique registry**
- ~12,000 people in a computerized registry maintained by the national IRL (CNRGS)
- Rare blood specificity systematically confirmed by CNRGS on blood samples
- Every newly enlisted person is given specific documents

RARE BLOOD CARD Recto

Centre National de Référence
pour les Groupes Sanguins

C.N.R.G.S.

(arrêté ministériel du 20.06.1985 - J.O. du 26.06.1985)

CARTE INDIVIDUELLE

**Phénotypes et/ou Génotypes
érythrocytaires rares**

(Extrait du fichier national des phénotypes érythrocytaires rares)

CNRGS : 20, rue Bouvier
BP 79 - 75522 Paris Cedex 11
Tél. : 01 55 25 12 12 (24 h/24)
Fax : 01 55 25 12 03
E-mail : cnrsgs@ints.fr

RARE BLOOD CARD

Verso

Centre National de Référence pour les Groupes Sanguins

Phénotypes et/ou Génotypes érythrocytaires rares

(document personnel)

Nom: PER

Née:

Prénom:T

Sexe: F

Date de naissance 19 /1 /1

Lieu de naissance

Adresse personnelle

GROUPE ABO:-1,-2,-3 (O)

Phénotype : YT:-1,2

Anticorps:

Anti-RH1,-RH2,-FY1,-JK2,-YT1

Correspondant

Madame le Docteur D
EFS PYRENEES MEDITERRANEE
Ave de Grande Bretagne
BP 3210
31027 TOULOUSE Cedex 3

Phénotype érythrocytaire

| RH | KEL | FY | JK | LE |
|-------------|---------|-----|-----|-----------|
| 1 2 3 4 5 8 | 1 2 3 4 | 1 2 | 1 2 | 1 2 |
| - - - + + | - | - + | + - | |
| MNS | P | LU | DO | YT CO XG |
| 1 2 3 4 | 1 | 1 2 | 1 2 | 1 2 1 2 1 |
| - + | | | - + | |

Génotype

Document établi le : 2011/08/16 à 22:04:46

Vous présentez un phénotype et/ou un génotype érythrocytaire (groupe sanguin) rare de type **YT:-1**

Il s'agit d'un caractère transmis génétiquement sans conséquence pathologique. Il impose cependant des précautions particulières en cas de transfusion (ou de grossesse) : celles-ci impliquent l'utilisation de votre propre sang ou de celui de donneurs présentant le même phénotype érythrocytaire rare. L'ensemble de ces sujets et des unités de sang congelé correspondantes sont répertoriés au Centre National de Référence pour les Groupes Sanguins. Il importe donc, afin que nous puissions assurer votre sécurité transfusionnelle et celle des sujets présentant le même phénotype érythrocytaire rare :

- **De mettre en place un programme de congélation d'unités de votre sang.**
- **De nous prévenir le plus rapidement possible, de tout problème médical, obstétrical ou chirurgical pouvant justifier des transfusions.**
- **De prévenir votre médecin traitant et, en cas d'hospitalisation, le personnel médical susceptible de vous prendre en charge** (médecin anesthésiste par exemple) en présentant ces documents.
- De rechercher dans votre **fratrie** (frères et sœurs) d'éventuels sujets présentant le même phénotype érythrocytaire rare.
- De nous communiquer le plus rapidement possible, tout changement d'état civil et de coordonnées (adresse ; n° de téléphone personnel et professionnel).

Nous vous adressons un **document personnel portant mention de l'ensemble de ces données, à conserver sur vous en permanence**. En cas de mentions erronées ou discordantes par rapport à d'autres documents nous vous serions reconnaissants de bien vouloir nous renvoyer ce document corrigé afin que nous puissions en éditer un nouveau.

THE NATIONAL RARE BLOOD BANK

- Created in the late 60s, currently operated at the logistical level by the National Blood Service (EFS)
- Implemented in order to quickly answer any rare blood request
- ~ 6,500 frozen RBC units / 1700 donors
- Long-term storage at -80°C (unlimited in France), with the high-glycerol technique (40%)
- **24/7 delivery of RBC units exclusively authorized by CNRGS (national IRL), independent from EFS**
- RBC units drawn after 2005 valid for 7 days (close-circuit device). 24h shelf life if drawn before 2005
- Cost: ~400 euros (vs. ~200 for a fresh unit)

| Rare type | Number of people registered | Number of donors | Number of cryopreserved RBC units |
|-------------------------------|-----------------------------|------------------|-----------------------------------|
| Fy(a-b-) | 5197 | 810 | 1922 |
| k- | 2422 | 163 | 849 |
| U- / U+ ^{var} | 752 | 175 | 518 |
| r'r' | 512 | 98 | 322 |
| Yt(a-) | 432 | 94 | 317 |
| Lu(b-) | 331 | 92 | 352 |
| r''r'' | 229 | 71 | 350 |
| Rh:-46 (R^NR^N) | 222 | 21 | 41 |
| Vel- | 185 | 45 | 286 |
| Bombay O _h | 137 | 26 | 96 |
| Kp(b-) | 131 | 41 | 216 |
| Ge:-2,3 | 121 | 19 | 76 |
| R _z R _z | 102 | 32 | 156 |
| p [Tj(a-)] | 84 | 26 | 98 |
| ... | | | |

EFFICIENCY OF THE RARE BLOOD BANK

- 849 k- RBC units are currently frozen, but only
17 O, Fy(a-), Jk(a-), S- (3 donors)
3 O, Fy(a-), Jk(a-), s- (1 donor)
- k- may not be considered “rare”, but the associated ABO, RH, FY, JK and MNS phenotypes must also be considered!

=> For rare types with a prevalence 2 - 4/1,000 (k-, Lu(b-)...) or those easily screened through donor testing (r'r', r''r'', Fy(a-b-),...): selection of A/O donors only, with a maximum of homozygous expressions for major antigens

IS Fy(a-b-) A RARE TYPE?

Data from the French National Registry:

- 83 Fy(a-b-) patients with anti-Fy3
- 24 Fy(a-b-) patients with anti-Fy5
- 105 Fy(a-b-) patients with anti-Fy^a (frequently precedes the making of anti-Fy3)

Anti-Fy3: autoantibody? Frequent HTRs reported

Possible confusion with anti-SI^a (KN4) since most Fy(a-b-) RBCs are KN:-4. However, reactivity of all our anti-Fy3 samples is enhanced in papain and trypsin techniques

Every Fy(a-b-) patient with anti-Fy^a, anti-Fy3 or anti-Fy5 is enlisted in the National Registry

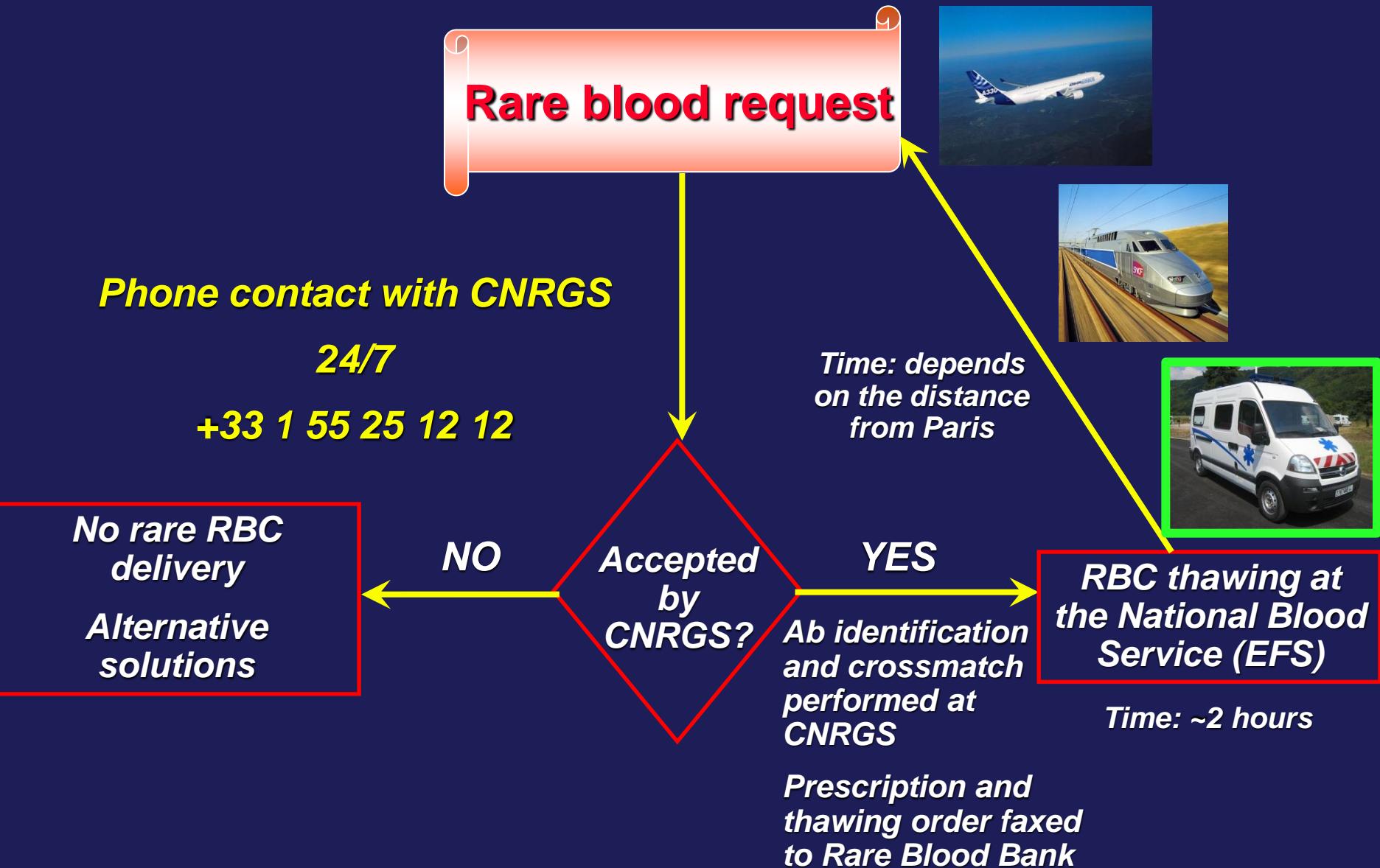
IS Fy(a-b-) A RARE TYPE?

Fy(a-b-) donors considered rare in France
only when associated to certain phenotypes:

- O/A, D+C-E-c+e+, K-, Jk(b-), S-, VS-, Js(a-)
- O/A, D+C-E-c+e+, K- being Jk(a-), S- or Jk(a-), s-
or Jk(b-), s-
- O, D-C-E-, K- with at least one homozygous
expression for Jk^a/Jk^b or S/s
- O, c-E-, K- with 2 homozygous expressions for
Jk^a/Jk^b and S/s
- O, C-e-, K-

No real concern yet for heterozygous HbS donors,
except for some pediatricians who do insist for it!

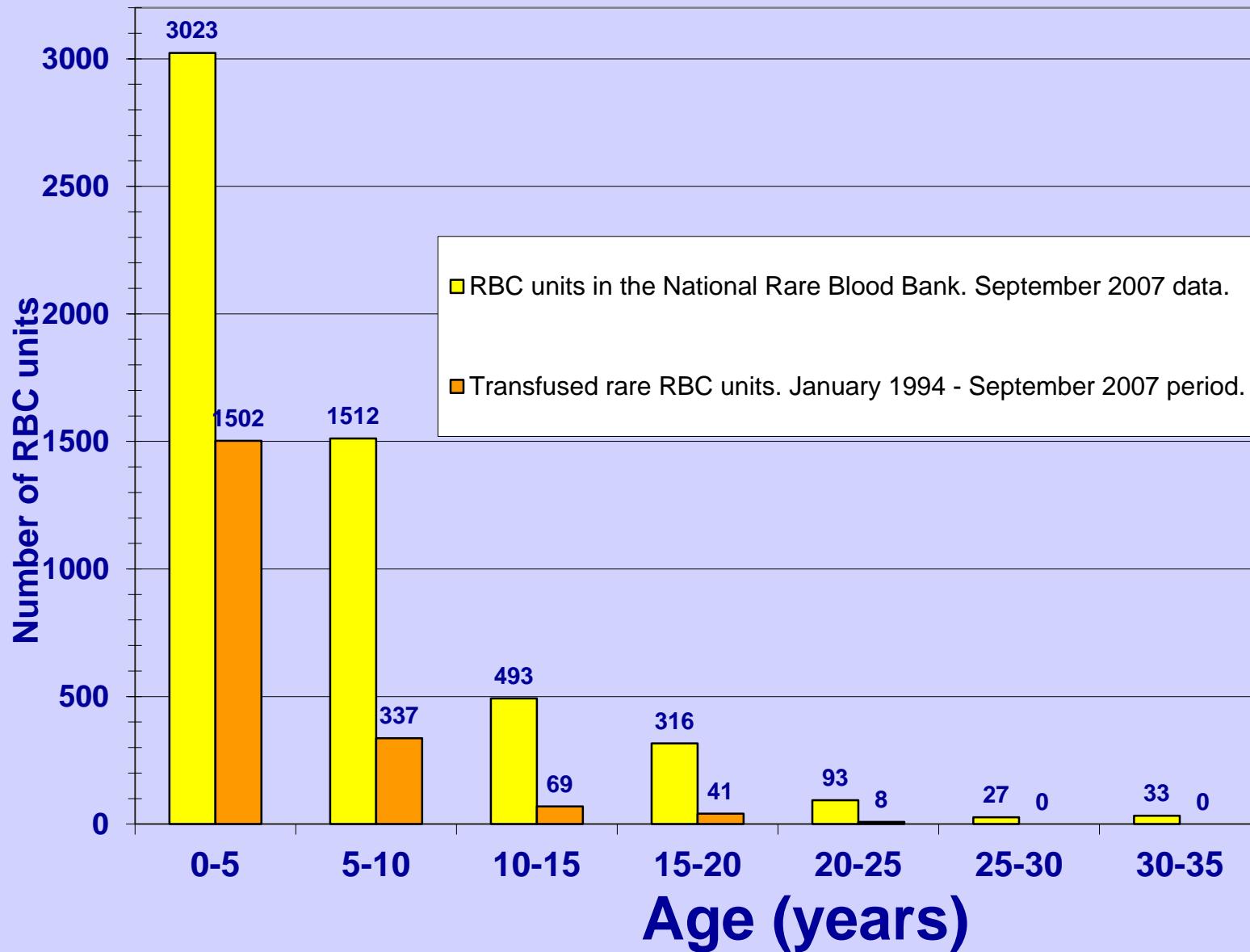
RARE BLOOD REQUEST PROCESS



Transfusion of rare cryopreserved red blood cell units stored at –80°C: the French experience

T. Peyrard, B.N. Pham, P.Y. Le Pennec, and P. Rouger

IMMUNOHEMATOLOGY, Volume 25, Number 1, 2009



THE FRENCH RARE BLOOD PROGRAM ACTIVITY

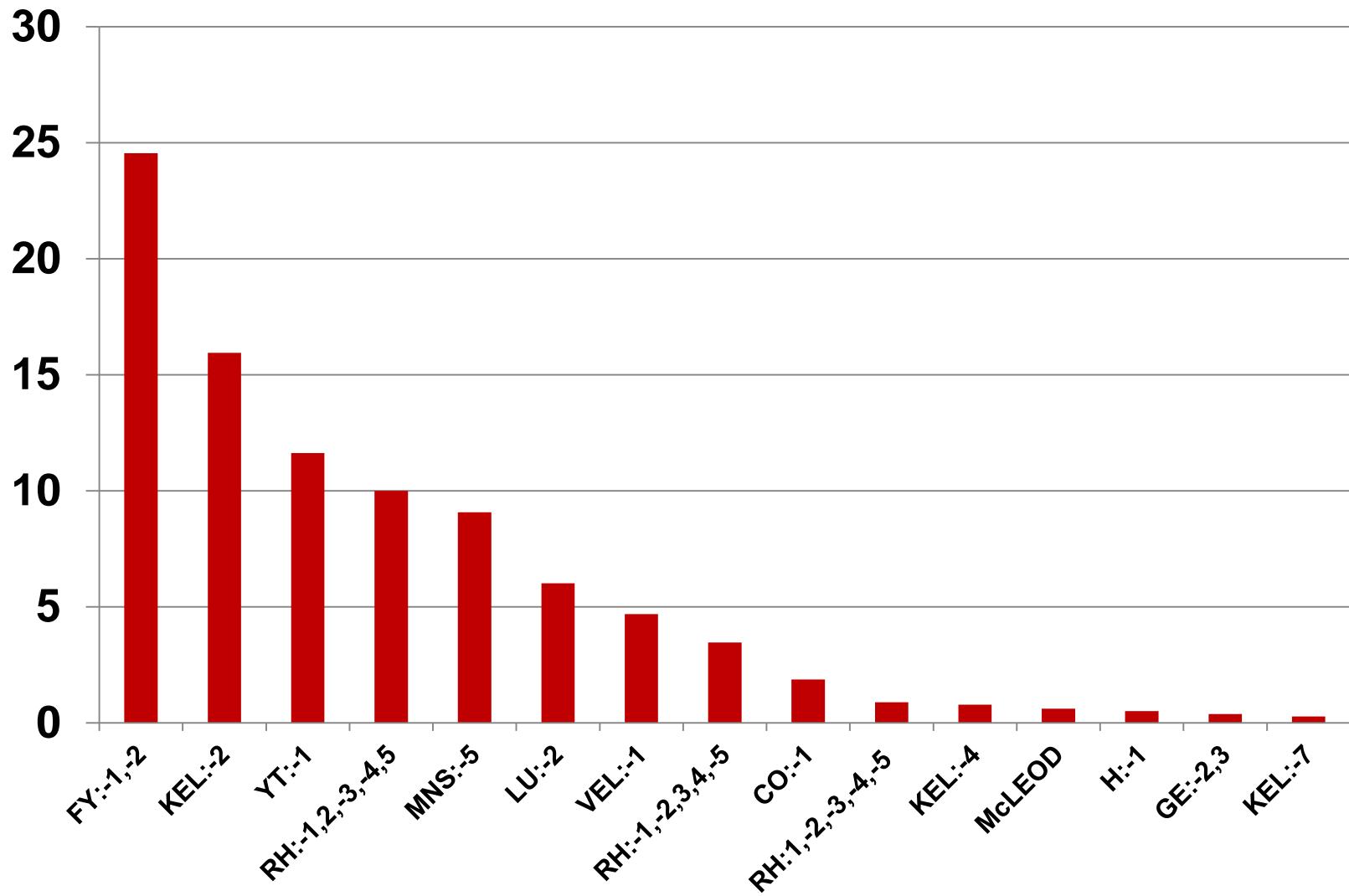
2011

- 56 patients transfused
- 309 RBC units delivered
(4.7 RBC units/million inhabitants/year)
- 148 transfusion episodes

1994-2012

- 35% delivered to patients with SCD
- 5 % shipped abroad: Austria, Belgium, Canada, Germany, Sweden, Switzerland

The top 15 rare blood specificities required between 1994 and 2011 (%)



EXCEPTIONAL TYPES

- Some people show more than one rare blood specificity!
- 5 persons of African origin, Fy(a-b-), with 2 rare blood types are known
 - Js(b-), Hy- anti-Hy
 - Lu(b-), Ge:-2,3 anti-Lu^b, anti-Ge2
 - Js(b-), r'r' anti-Js^b, anti-c
 - 2 U-, R^NR^N no antibody
- 17 Caucasian people with 2 rare blood types are known

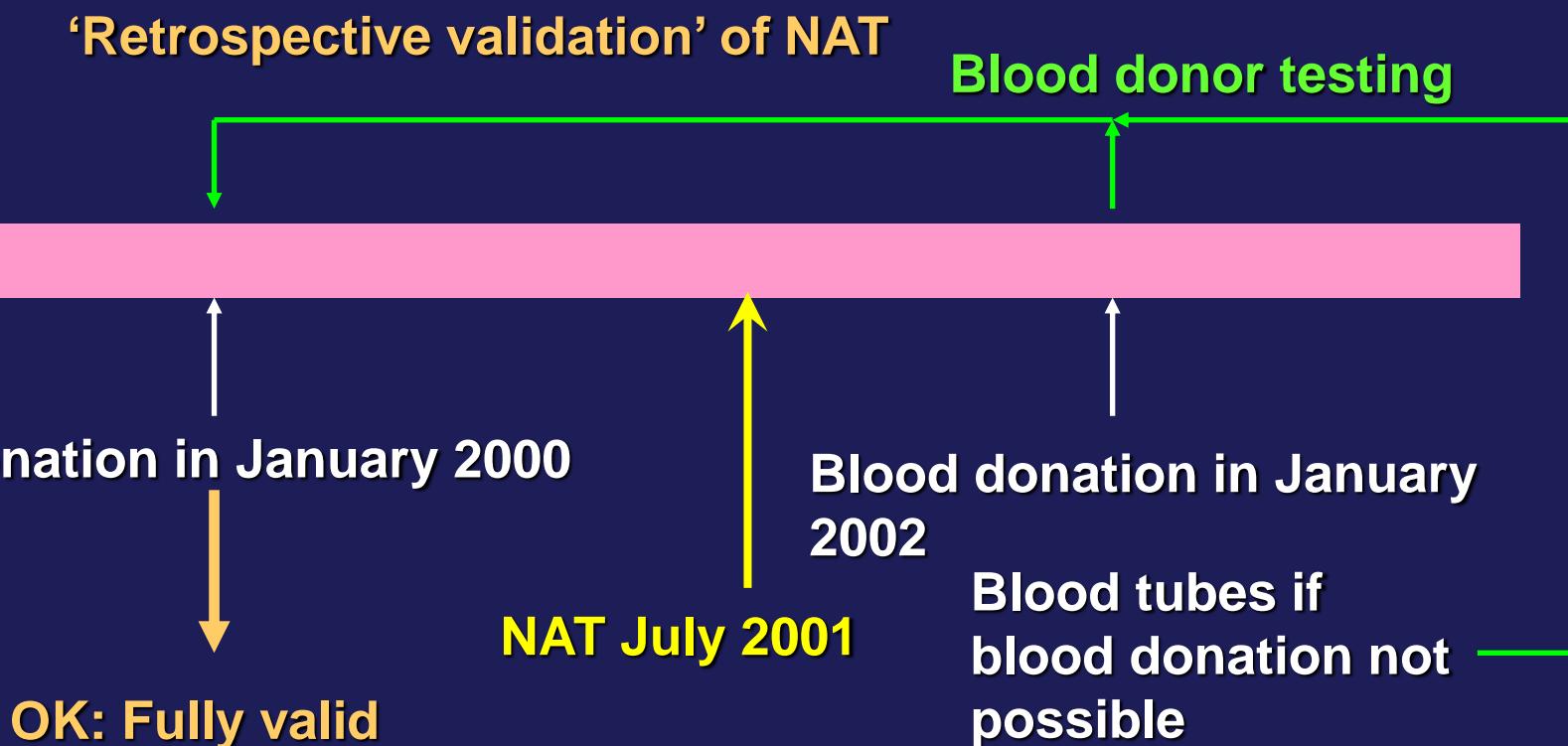
| First rare blood type | Second rare blood type | Alloantibody(ies) | Number of frozen RBC units |
|-----------------------|-------------------------------|--|----------------------------|
| k- | R _z R _z | - | 0 |
| k- | r"r" | - | 0 |
| k- | r'r' | - | 0 |
| k- | Lu(b-) | Anti-Lu ^b | 2 |
| k- | Lu(b-) | - | 2 |
| k- | Lu(b-) | - | 0 |
| k- | Lu(b-) | Anti-Lu ^b | 0 |
| k- | Yt(a-) | Anti-k, anti-Yt ^a , anti-Fy ^a , anti-Jk ^b | 8 |
| k- | Yt(a-) | Anti-Yt ^a | 0 |
| k- | Vel- | - | 9 |
| Yt(a-) | Jk(a-b-) | Anti-Jk3 | 7 |
| Yt(a-) | Vel- | Anti-Vel | 9 |
| Lu(b-) | r _y r _y | - | 2 |
| Lu(b-) | Kp(b-) | Anti-Kp ^b | 0 |
| Ge:-2,3 | Jr(a-) | Anti-Jr ^a | 0 |
| Ge:-2,3 | Jr(a-) | - | 1 |
| Vel- | Jr(a-) | Anti-Vel, anti-Jr ^a | 0 |

BLOOD DONOR INFECTIOUS DISEASE TESTING

Drawing blood in donors being positive for infectious diseases, except HIV, is allowed but only for exceptional types

- Such blood is used only if no alternative solution exists
- Informed consent of the patient and clinician is required, along with written authorization of CEO (or representative) of both INTS and EFS
- Most frequent situation is a positive malaria antibody test for rare types in Africans

NAT IMPLEMENTATION IN 2001



NAT IMPLEMENTATION IN 2001

Blood donation in
January 2000

Discard the RBC unit?

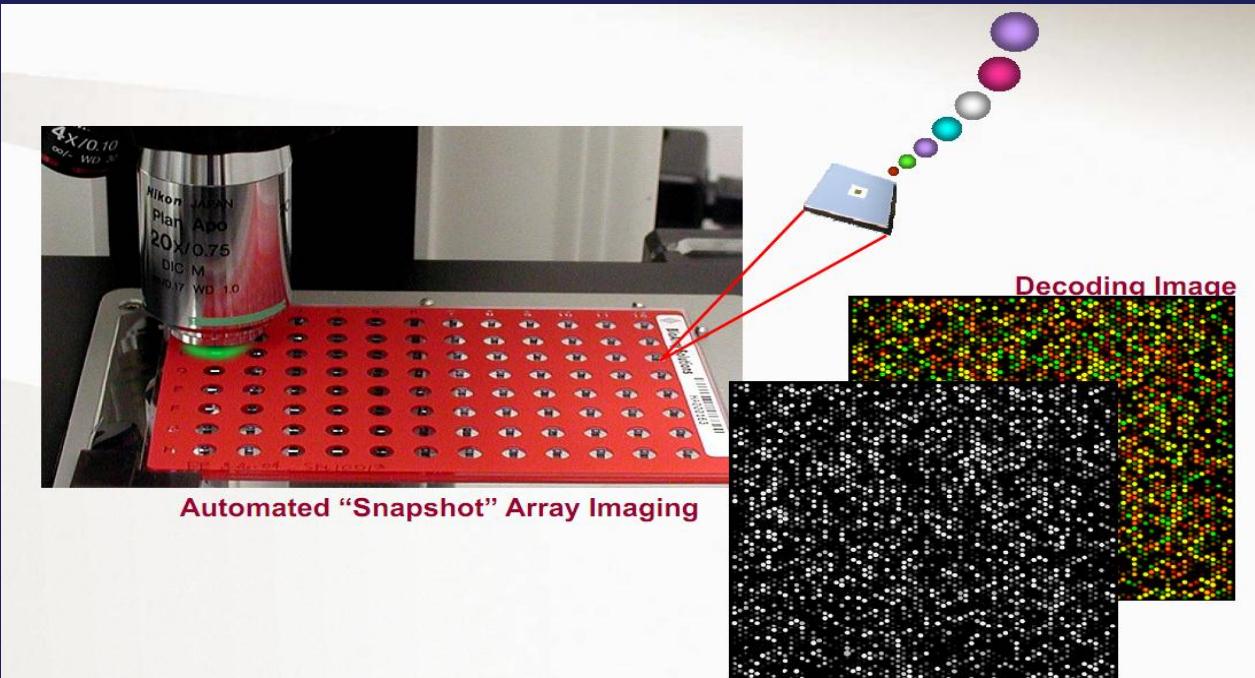
Blood donor not
contactable

NAT July 2001

May be an ethical issue!

THE FUTURE

SHORT TERM: TARGETED MOLECULAR TYPING



Systematic genotyping of both repeat donors of African descent and sickle cell patients:

- VS, Js^a, Do^a/Do^b status in Fy(a-b-) people
- Distinction of U- and U+^{var} in S-s- people: anti-U made by U- may be incompatible with U+^{var} RBCs!

LONG TERM

Cultured red blood cells?

Banking of Pluripotent Adult Stem Cells as an Unlimited Source for Red Blood Cell Production: Potential Applications for Alloimmunized Patients and Rare Blood Challenges

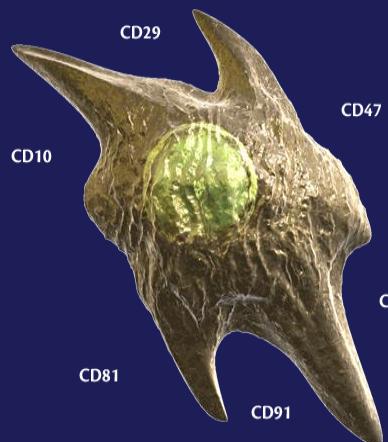
Thierry Peyrard, Laurent Bardiaux, Claire Krause, Ladan Kobari, Hélène Lapillonne,
Georges Andreu, and Luc Douay

Transfusion Medicine Reviews, Vol 25, No 3 (July), 2011: pp 206-216

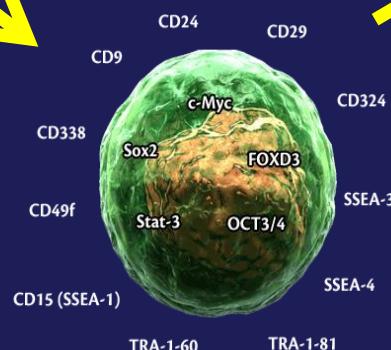
- **CD34+ stem cells through apheresis**
- **Human induced pluripotent stem cells (hiPSC)**

HUMAN INDUCED PLURIPOTENT STEM CELLS (hiPSCs)

Fibroblast

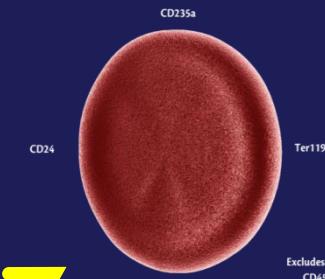


Dedifferentiation



Pluripotent
stem cell

RBC



Reprogramming

LONG TERM

Rare types and sickle cell disease

One single donor “clone” of cultured red blood cells, type O, D-C-E-c+e+, K-, Fy(a-b-), Jk(a+b-), M-N+S-s-U-, VS-, Js(a-), Do(a-), Le(a-b-) would have met 73% of the needs during the past 15 years

Exceptional “null” types : very useful!

Rh_{null} : compatible with all rare RH types

K_o : compatible with all rare KEL types

...

LONG TERM

Imagine that we could make, from a
O, Rh_{null}, K- donor, hundred liters of RBCs!
Science fiction scenario?
This might be possible in the future!

Proof of principle for transfusion of in vitro-generated red blood cells

*Marie-Catherine Giarratana,^{1,2} *Hélène Rouard,^{3,4} Agnès Dumont,⁵ Laurent Kiger,⁶ Innocent Safeukui,⁷ Pierre-Yves Le Pennec,⁸ Sabine François,^{1,2,9} Germain Trugnan,¹⁰ Thierry Peyrard,⁸ Tiffany Marie,¹⁻³ Séverine Jolly,¹⁻³ Nicolas Hebert,¹⁻³ Christelle Mazurier,¹⁻³ Nathalie Mario,¹¹ Laurence Harmand,¹⁻³ Hélène Lapillonne,^{1,2,12} Jean-Yves Devaux,⁵ and Luc Douay¹⁻¹³.

Blood 2011

Cultured human RBCs proven to be functional in vivo have been produced, yet in very small quantity



Merci
beaucoup
pour le sang

