Malaria donor deferral policy in France: French experience with malaria antibody screening

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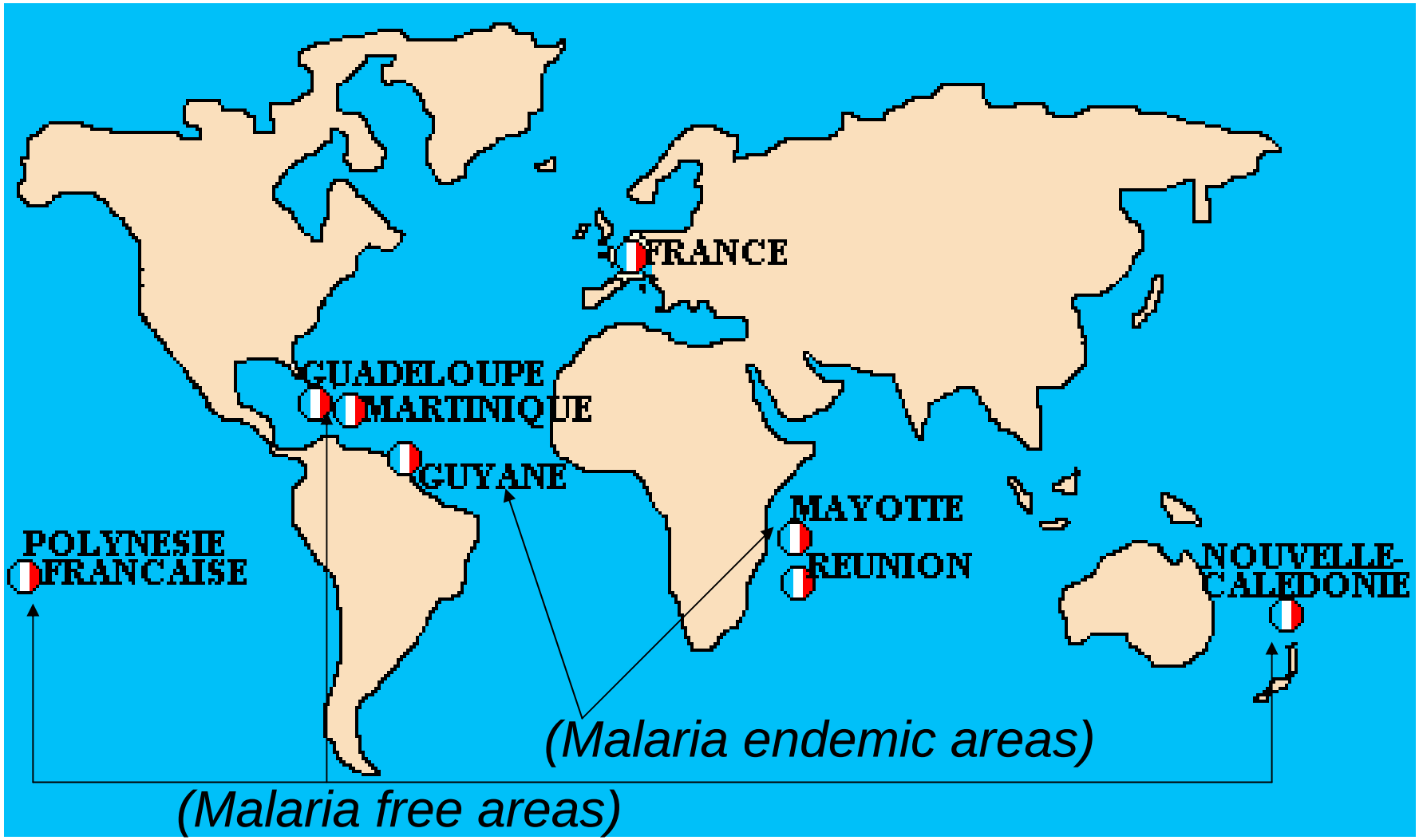
The French situation

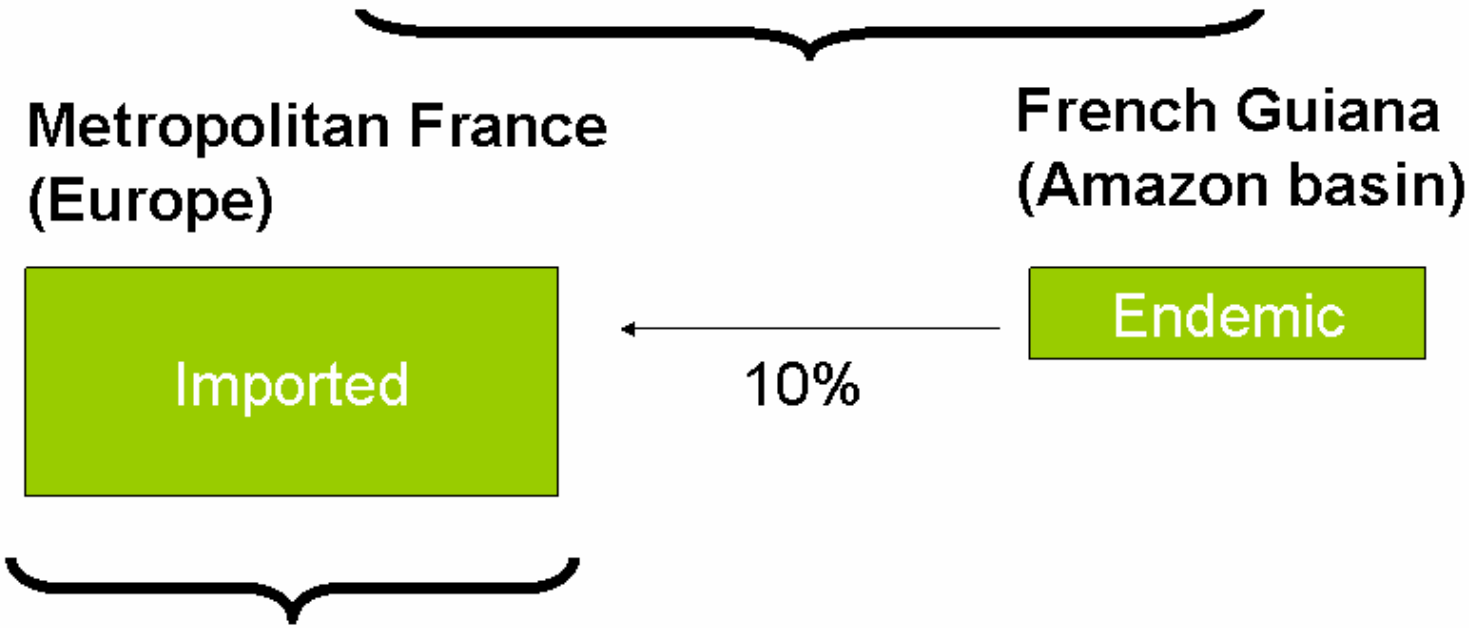
- **Increasing immigration** (7.4% of individuals living in France in 1999); 39.3% of immigrants originate from Africa; Of approx. 136.000 immigrants/year (2003), 90.000 came from Maghreb or Black Africa => approx. **40.000 from Central & West Africa**;
- **Increasing circulation of individuals**: in 2003, France delivered approx. 307.000 visas to travelers from **Sub-Saharian Africa** (including for transit and short stays)

- **Increasing travel and leisure**: more than 3 million people living in France travel each year to **tropical areas** for vacationing, business or visiting relatives
- **The 1st cause of fever in returning travelers** (from tropical areas) **is malaria** (42.5% in a French survey in Marseille,BEH-2006)



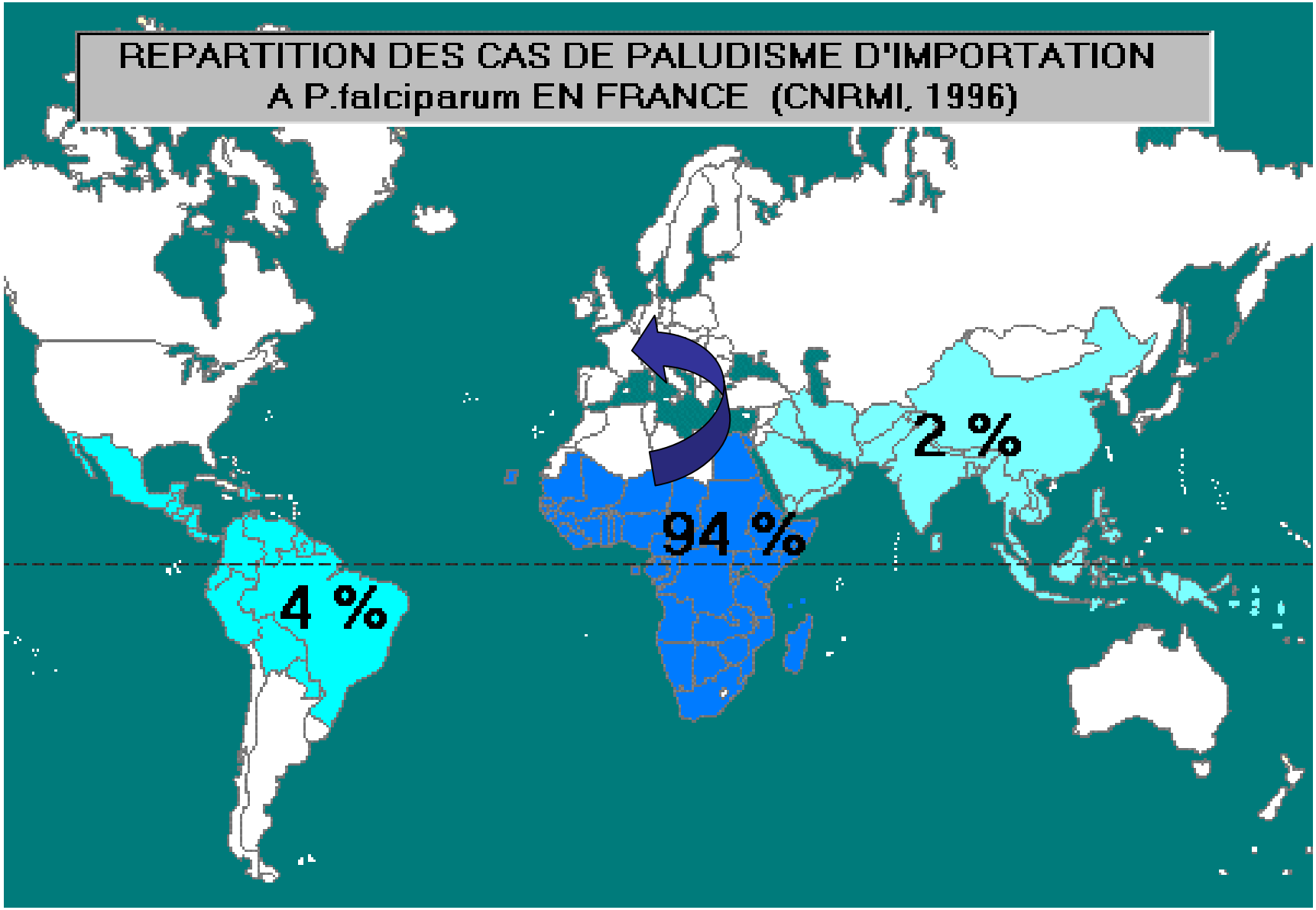
France is not restricted to te European territory…

Malaria in France



Over **7.000 imported cases** p. y. in France (2005):

80% from Africa, 10% from Comores & Mayotte, less than 1% from Guiana



Imported malaria in France

Malaria in France

- **France records most imported malaria cases than any other European country** (≥7,000 cases p. year; Danis, 2005; Legros 2005)
- **≥ 80% imported cases from 13 West & Central African countries** + 10 % from Comores and Mayotte (Mayotte is a French District) + a few % from French Guiana.
- **≥ 75% occur in Africans residing in France**
- **83.5% *P. falciparum***, 6.5 % *P. ovale*, 4.5 % *P. vivax* (French Guiana) & 1.6 % *P. malariae*
- 5% cases are ‘’severe’’

Transfusion transmitted malarial infection

Endemic,
« Southern type »

Very frequent
Difficult to evaluate

Non-endemic,
« Northern type »

Incidental

-Europe (incl. France)
-Northern America (incl. US and Canada)

Transfusion transmitted malaria always severe, often lethal

Transfusion-transmitted malaria observed cases over the past 10 years (after H.W. Reesink, 2004)

France	1	Tunisia	1
Ireland	0	Israel	1
Italy	7	Japan	1
Spain	0	UK	2
Switzerland	0	Canada	3
Germany	0	USA	≥10?

History of transfusion-transmitted malaria in France (after H. Rech, Montpellier, Fr; 2000)

- From 1960 to 1989: approx. 120 reported cases, half of which having occurred between 1975-1989)
- 1990: 3 cases in the EU, of which 1 in France

- Other cases in France since then:
  - 1 in 1993,
  - 1 doubtful case in 1998,
  - 1 near miss case in 1999,
  - 1 lethal case in 2002 (Of note: the 2003 British case was very similar to the 2002 French case).

Blood collection in France

- Anonymous, voluntary, non-profit, neither direct nor indirect benefit
- One single governmental organization - unified in 2000 - called “Établissement Français du Sang”
- Subdivided in 14 regions in Metropolitan France and 4 Overseas Blood Centers

- **Collection of:**
  - 2.2 million units of whole blood per year, relatively stable overtime
  - 218,000 plasma apheresis procedures, increasing over time
  - 169,000 platelet apheresis procedures, increasing overtime

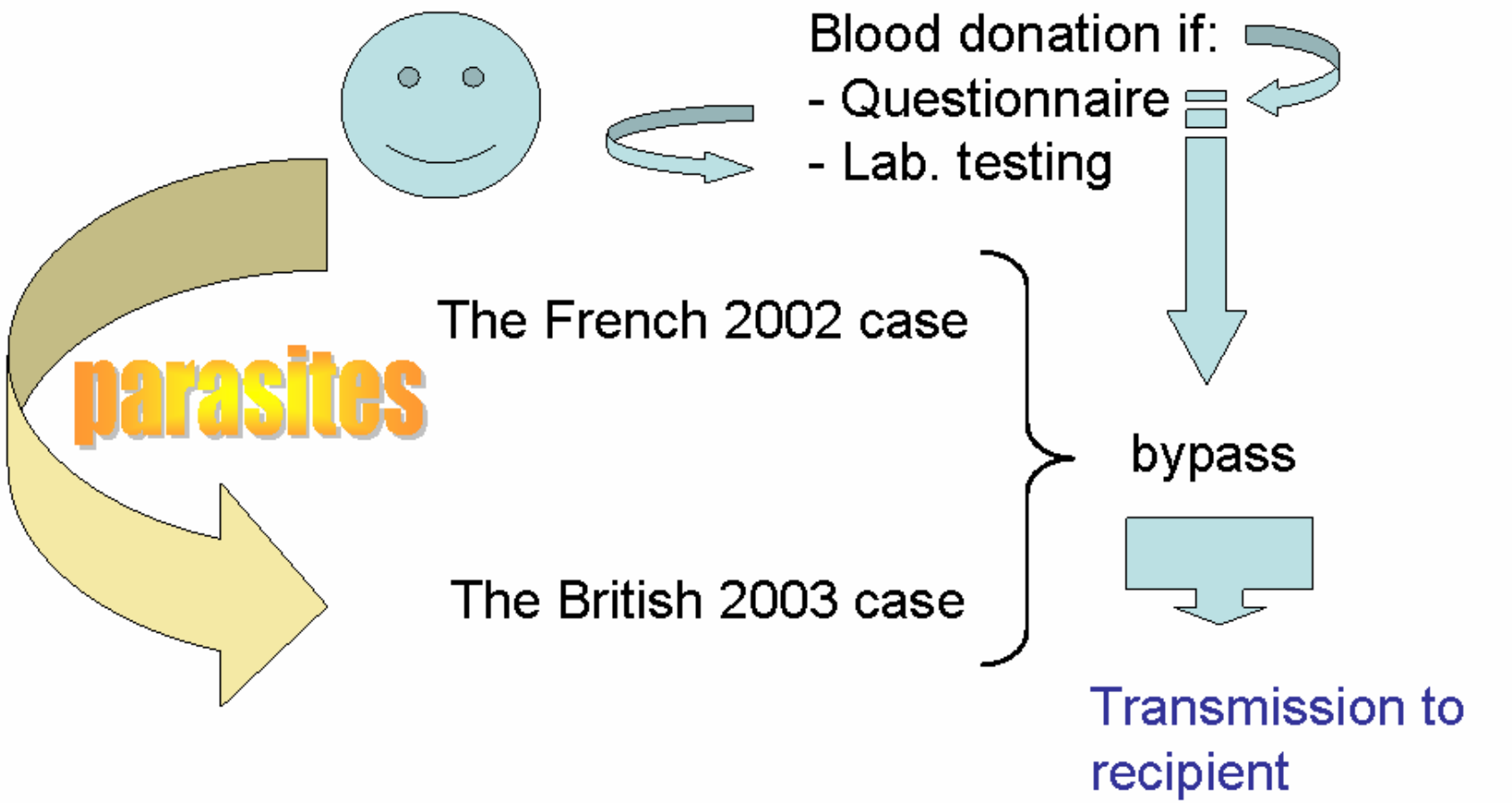
***Plasmodiae* can be transmitted by labile products** (RBC packs; PLT packs)
They do not survive freezing (therapeutic or fractionated plasma)

Transfusion-transmitted malaria prevention in France

- **Since the early 90'**
  - Information and incitation to self-exclusion in case of self history of malaria
  - Questionnaire about malaria and exotic travels (1994)
  - **Anti-malaria antibody testing by indirect single test** (recommended: immunofluorescence/IFA) (1995)

Safe enough? 

Safe enough?


Blood donation if:
- Questionnaire
- Lab. testing
parasites
The French 2002 case
The British 2003 case
bypass
Transmission to recipient

Serology/IFA

- Implemented in 1995
- **IFA**
  - Not standardized between the Biological Qualification platforms
  - Could be performed
    - Either in the EFS platforms
    - Or trusted with University Hospital Platforms
  - Results based on a “+” or “-” basis
- *Caveats*
  - IFA difficult to perform and standardize - even within one platform
  - Difficult to trace if trusted with outside platforms
  - Numerous false positives
  - Do not detect Abs to species other than *P. falciparum*

Of note…

- **Lab testing = based on serology**
  - **Malaria and serology do not necessarily fit very well** (see the recent TT-malaria case in the US reported by Purdy in '*Transfusion*', 2004)
  - **Parasites and serology do not fit very well in general** (Garraud, '*TCB*': 2002, 2005)
  - **Malaria and parasites: '≠'** (Garraud, '*Transfusion*', in press)
  - ***P. falciparum*** ±, but *P. vivax* and *P. malariae* (and *P. ovale*) ???
  - **Silent serological period** whatever the test used (variable; depends on individual, prophylaxis, *Plasmodium* species…)
- **=> NAT? --- Ag? --- ??? ---**

Needs in term of serology to qualify blood => blood safety

- Robustness
- Reliability
- Sensitivity
- Specificity
- Automation is an advantage
- ----------
- Acceptability:
  - False positives: (but risk of blood product shortage)
  - No false negatives: risk of infectivity

Biological qualification of Blood products is not Clinical Biology:

-different objectives

-different requirements

Safety in question:
After the occurrence of the 2002 case => Revised measures in France (2005-2006)

- **Aug. 2002**: all natives (or equivalent) from endemic countries --> serology (whatever the time elapsed since return)
  - Doubled the # of tests
  - Necessitates automation
- Revision of certain measures after the 2002 French case (AFSSaPS/EFS consensus) (**2005**)
  - AFSSaPS is the French National Regulation and Authorisation Authority for Drugs and all products regarding health products (including cosmetics etc.);
  - => **Blood**, Cells, Tissues and grafts
- **Implementation of anti-malaria antibody testing by indirect single ELISA test (2005)**
- Implementation of the EU directive and novel consensus (EFS) (**2006**)
- + Brainstorming about procedures of pathogen-inactivation! (safety, implementation and hemovigilance trials: platelets, plasma: Amotosalem, Riboflavin)

1. Revision of deferral policy

3 situations	Policy	Lab. testing
Reporting of malaria	-Permanent deferral for cellular products -Plasma for fractionation	-No need of serology
-Reported travel in endemic area (listed) - & Less than 3 mo - & Symptomless	-Temporary deferral for 4 mo for cellular products -Plasma for fractionation	-Serology to qualify the 1st donation during the period 4 mo -- 3 y after return (one neg test: OK)
-Immigrant from endemic country -or traveler for > 3 consecutive mo -or traveler w. symptoms less than 4 mo after return	-Temporary deferral for 4 mo for cellular products -Plasma for fractionation -From 4 mo to 3 y: if symptomless & neg serology: OK -OK after 3 y	-Serology to qualify all donations during the period 4 mo -- 3 y after return

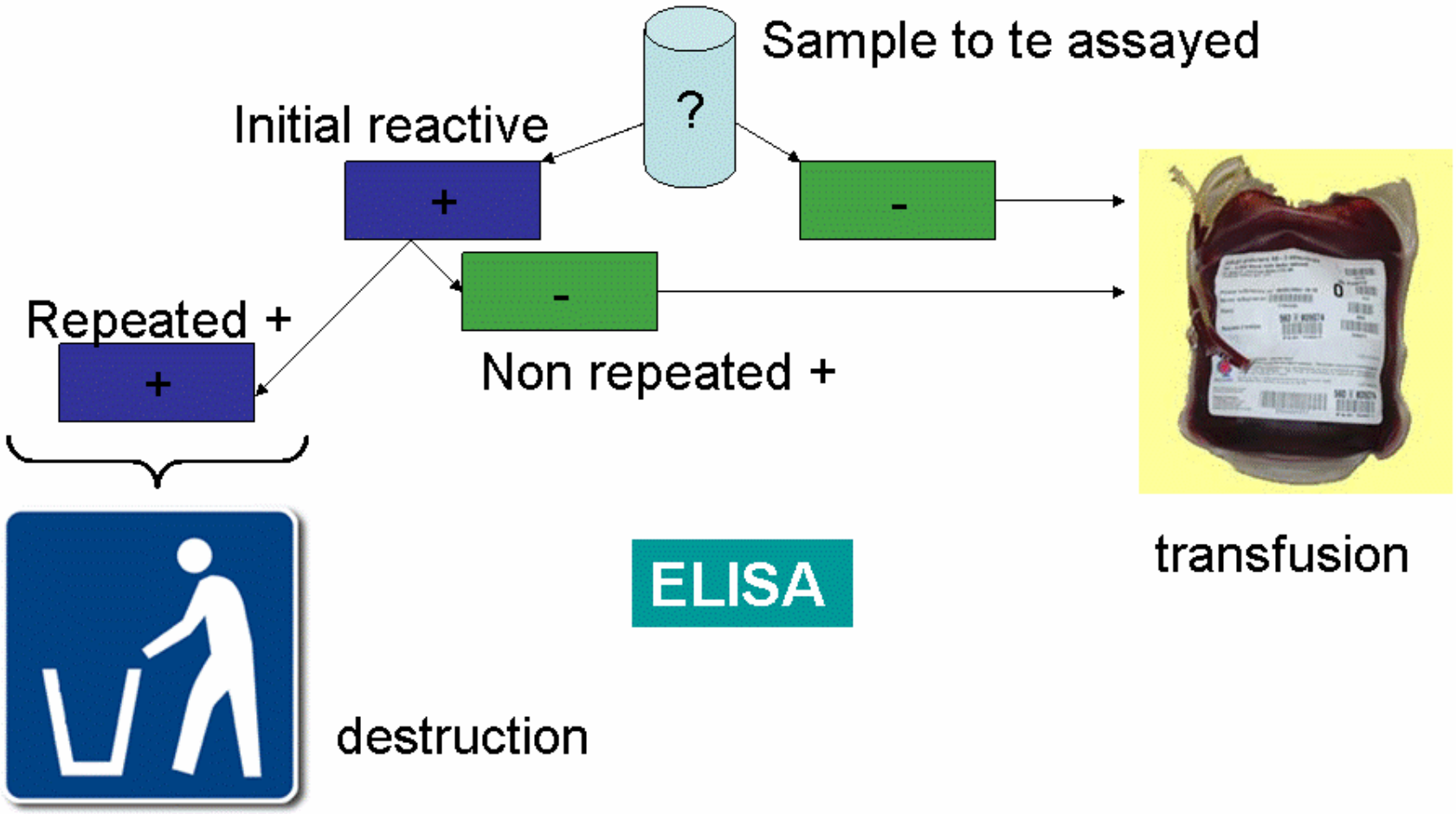
2. Revision of lab testing (serology)

- Observational period (2004-2005)
  - To obtain information on alternative assays (NAT/PCR, Ag)
  - To evaluate both ELISA kits and automated ELISA platforms
  - To compare to IFA
- Test period (2005)
  - Evaluation of 2 CE-marked ELISA kits (from Diagast™, Fr. and from Diamed™, CH.)
  - Large scale comparison study of ELISA vs IFA
    - EFS: 4,000 samples from exposed and non-exposed + certain tricky samples from collections
  - External expertise commissioned
    - IPPTS: 10,600 samples from Pf and/or Pv exposed individuals =>IFA vs ELISA
    - Exploration of false positives and negatives by means of PCR

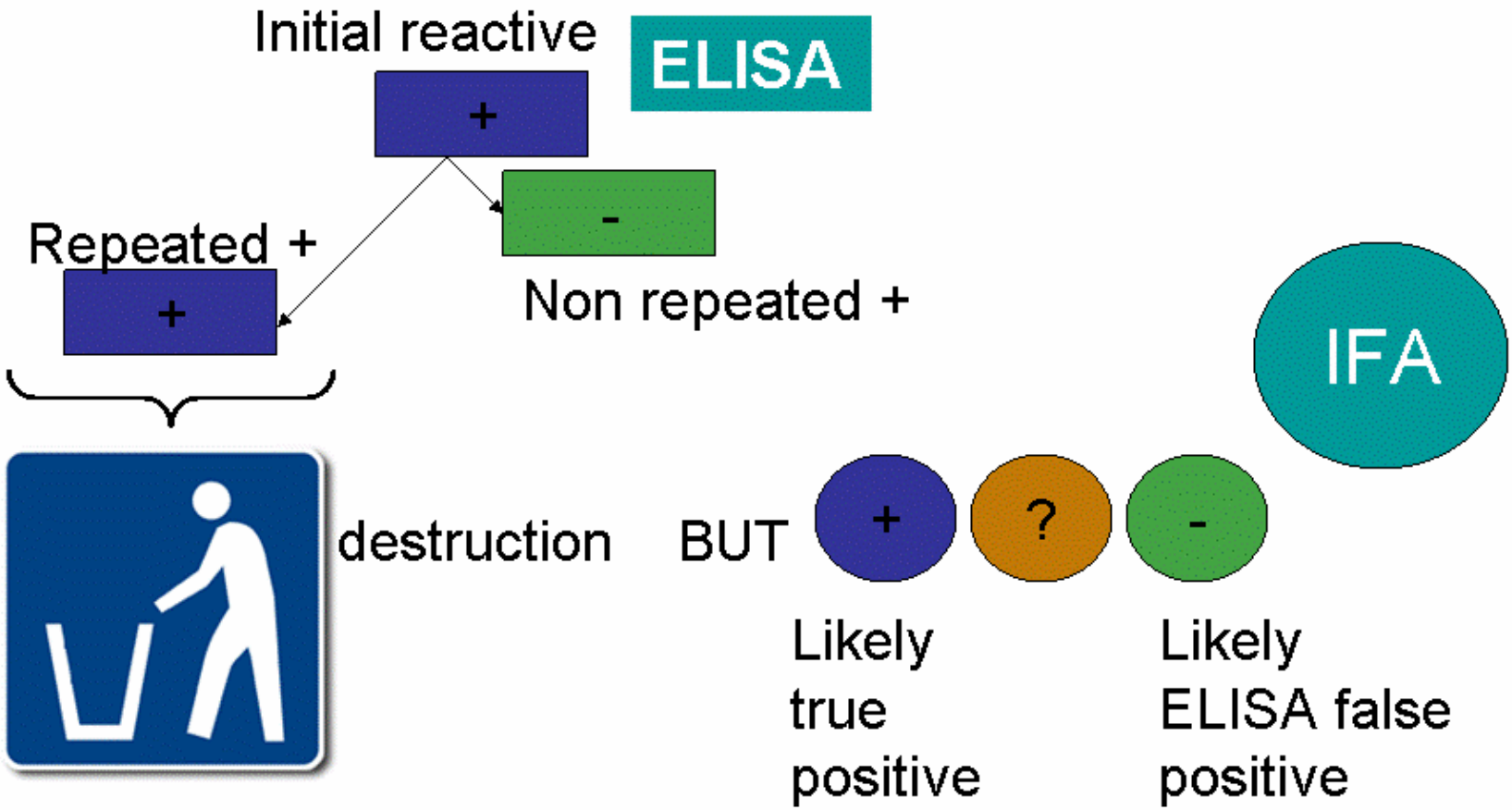
Selection of an ELISA kit

- CE-marked
- Approved by Regulation authority and experts
- One national market (EFS)
  - The Diagast™ ELISA (4 unidentified rec. Ags) did not pass the evaluation
  - The Diamed™ ELISA (x rec. Ags from Pf and one? from Pv) passed the evaluation
- Diamed™ ELISA vs IFA
  - Same sensitivity
  - Limited # of false negatives
  - False ELISA+ different than false IFA+ => ?
  - Detects Abs to non-Pf species contrary to IFA, in particular Abs to Pv
  - Detects lower Ab titers than IFA (to be confirmed in an even larger series)

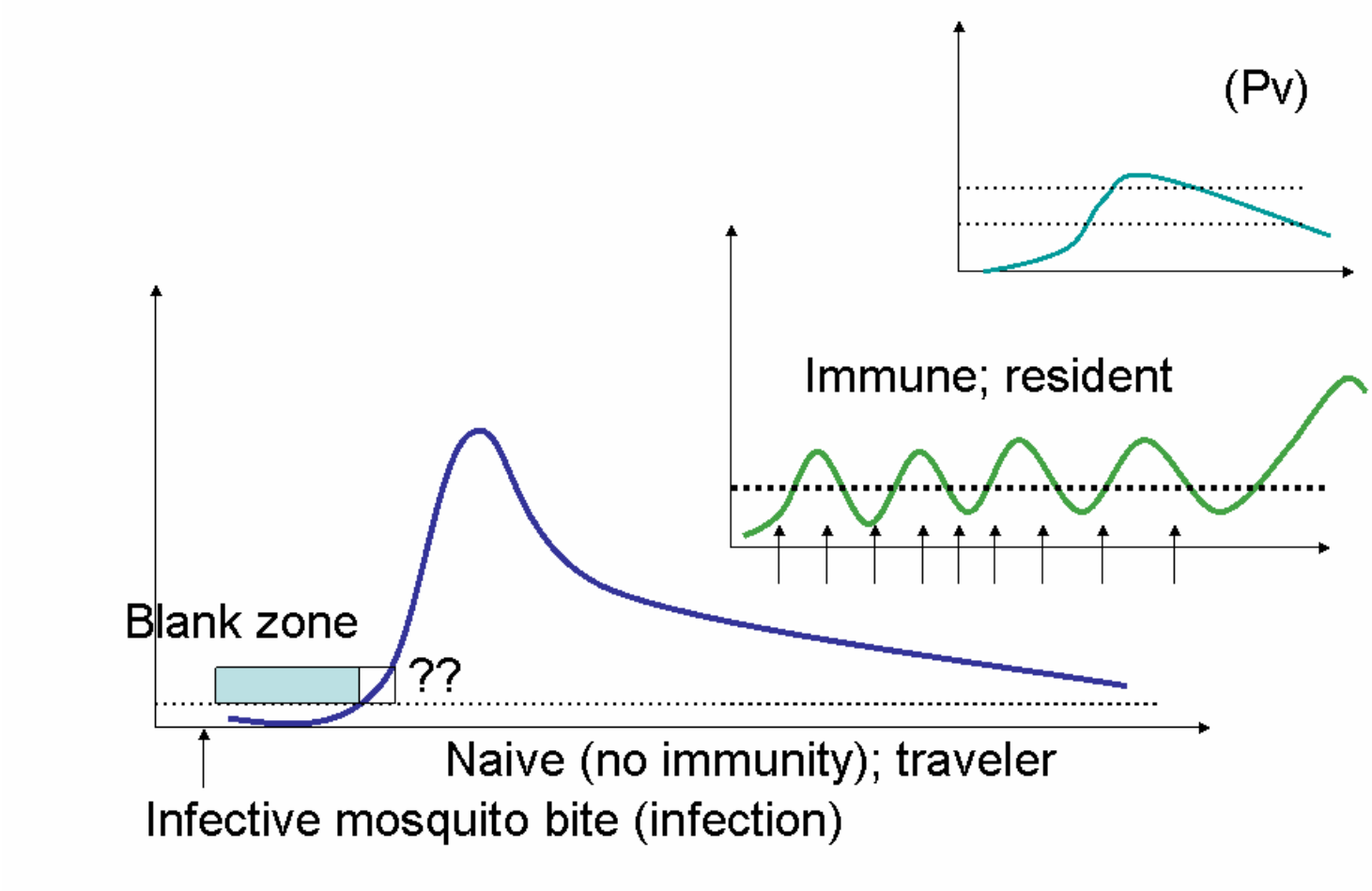
Malaria serology: Decision algorithm
ELISA: qualifying test



Information to blood donor: IFA (not qualifying test)



Interpreting serology (Pf)



Lab. results

- X serology assays per year in France
- Y positive (x%)
- Doubts subsist on
  - Robustness
  - Window period
  - Detection of Abs to Ags on species other than *P. falciparum*
- ----------
- Medical interview and lab. testing: Discards approx. 10% total blood donations

Conclusion

- The measures taken in France and in most European countries to prevent Transfusion-Transmitted malarial infection are [almost] sufficient
  - The « zero » risk does not exist!

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