



# MDR-TB national consilium : principles, organization, results

Vincent Jarlier MD PhD

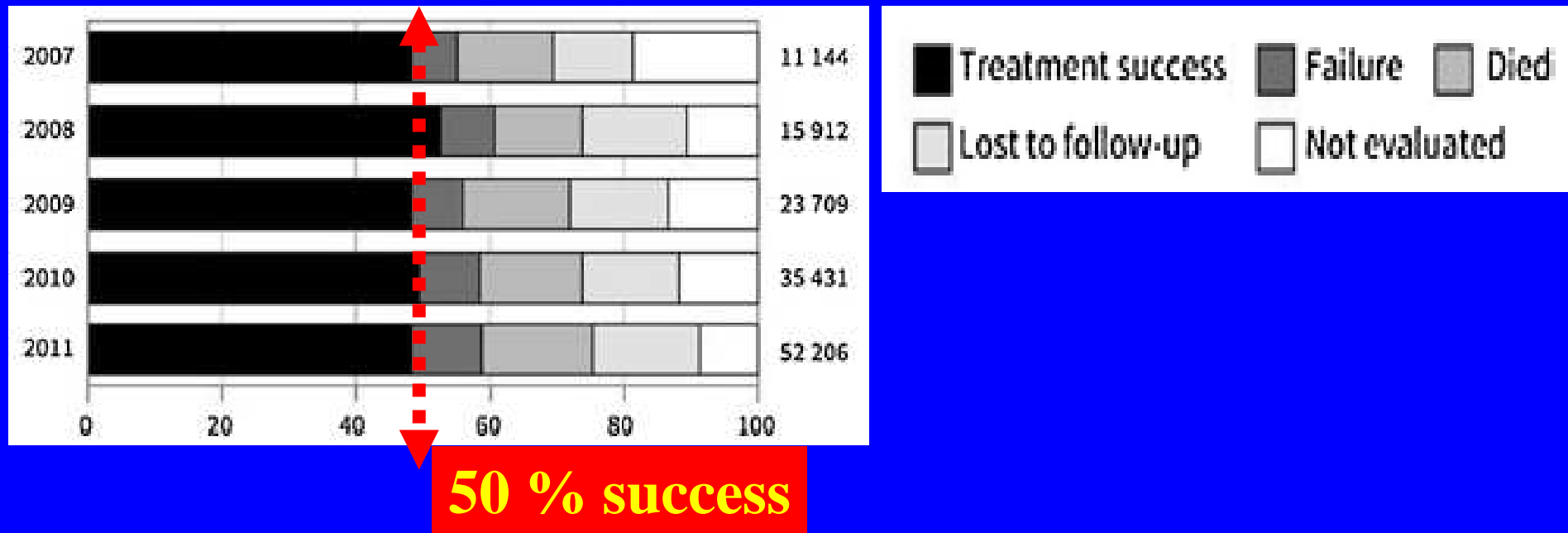
INSERM U1135 CR7, UPMC University Paris 6, France

National reference Center

for mycobacteria and resistance to antituberculous agents

# Results of MDR-TB cases treatment

## 1. WHO report 2014



## 2. Metanalysis by Ahuja, Plos Med 2012

- 32 observational studies
- 9,153 MDR-TB cases
- Success 54%

# Causes of poor outcome in MDR-TB

- Limited number of active drugs
- Few very active drugs (FQ, AMG)
- Long treatment → adherence problems
- Limited capacities for drug susceptibility testing
- Limited experience in MDR-TB management beside specialists
- Efficient regimens difficult (tricky) to design

# How to improve MDR-TB management: TB-consilium

- Advocated by WHO
- Specialized team
- Multidisciplinary team
- Endorsed by health authorities
- Available to every physicians
- Free and rapid expertise

# How to improve MDR-TB management

Supporting clinical management of the difficult-to-treat TB cases:  
the ERS-WHO TB Consilium

Lia D'Ambrosio<sup>a</sup>, Marina Tadolini<sup>b</sup>, Rosella Centis<sup>a</sup>, Raquel Duarte<sup>c</sup>, Giovanni Sotgiu<sup>d</sup>,  
Stefano Aliberti<sup>e</sup>, Masoud Dara<sup>f</sup>, Giovanni Battista Migliori<sup>a,\*</sup>

## 1. International ERS/WHO consilium

- Launched 2012
- Free
- Multilingual
- Internet-based
- Provides suggestions

**Data from the 1st 70 cases submitted (IJID 2015)**

Country: India 27%, Italy 23%, UK 16%

Strain status: S 27%, R 10%, **MDR 60%**

# How to improve MDR-TB management

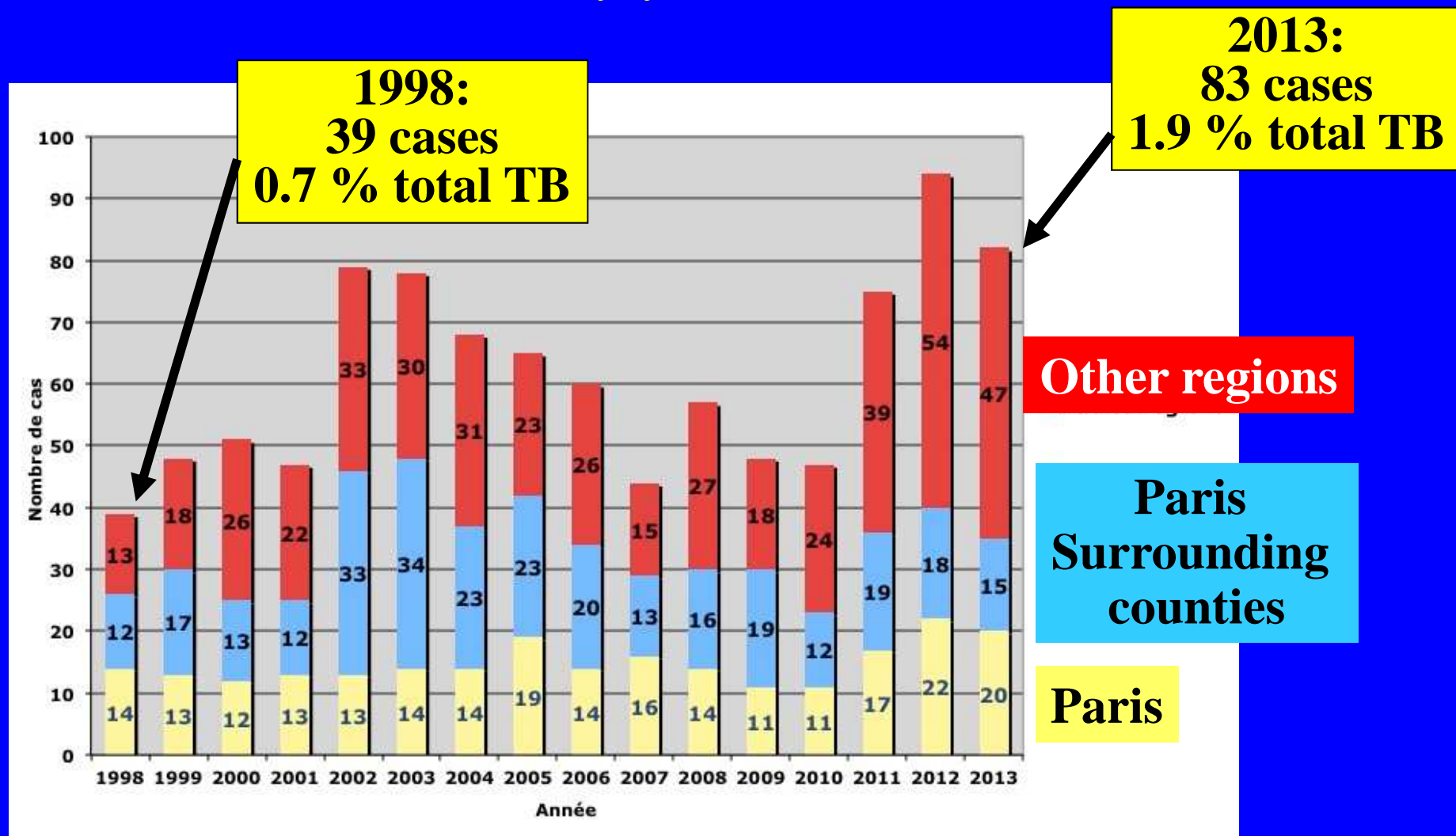
## 2. National consilium

- Particularly interesting in low incidence countries due to the lack of expertise (bacteriology & therapeutics) in MDR-TB
- Available in some of such countries
  - UK
  - Germany
  - France

# TB in France today

- ~ 5000 culture + cases / year
- 3/4 pulmonary forms
- 1/2 smear +
- ~ 8 % previous treatment
- ~ 6% HIV +

# Evolution of MDR cases France 1998-2013





# Characteristics of MDR-TB cases France 1992-2010

|                         | 1992-95    | 1996-00    | 2001-05    | 2006-10    |
|-------------------------|------------|------------|------------|------------|
| N cases                 | 186        | 192        | 339        | 257        |
| <b>Median age ↘</b>     | <b>39y</b> | <b>37y</b> | <b>31y</b> | <b>32y</b> |
| <b>Male ↘</b>           | <b>74%</b> | <b>65%</b> | <b>61%</b> | <b>57%</b> |
| Pulmonary TB            | 92%        | 94%        | 90%        | 86%        |
| Smear +                 | 56%        | 63%        | 62%        | 52%        |
| <b>HIV+ ↘</b>           | <b>19%</b> | <b>19%</b> | <b>17%</b> | <b>11%</b> |
| <b>Previous Tt ↘ ↘</b>  | <b>72%</b> | <b>55%</b> | <b>39%</b> | <b>32%</b> |
| <b>Foreign born ↗ ↗</b> | <b>52%</b> | <b>62%</b> | <b>79%</b> | <b>84%</b> |

# TB- consilium in France

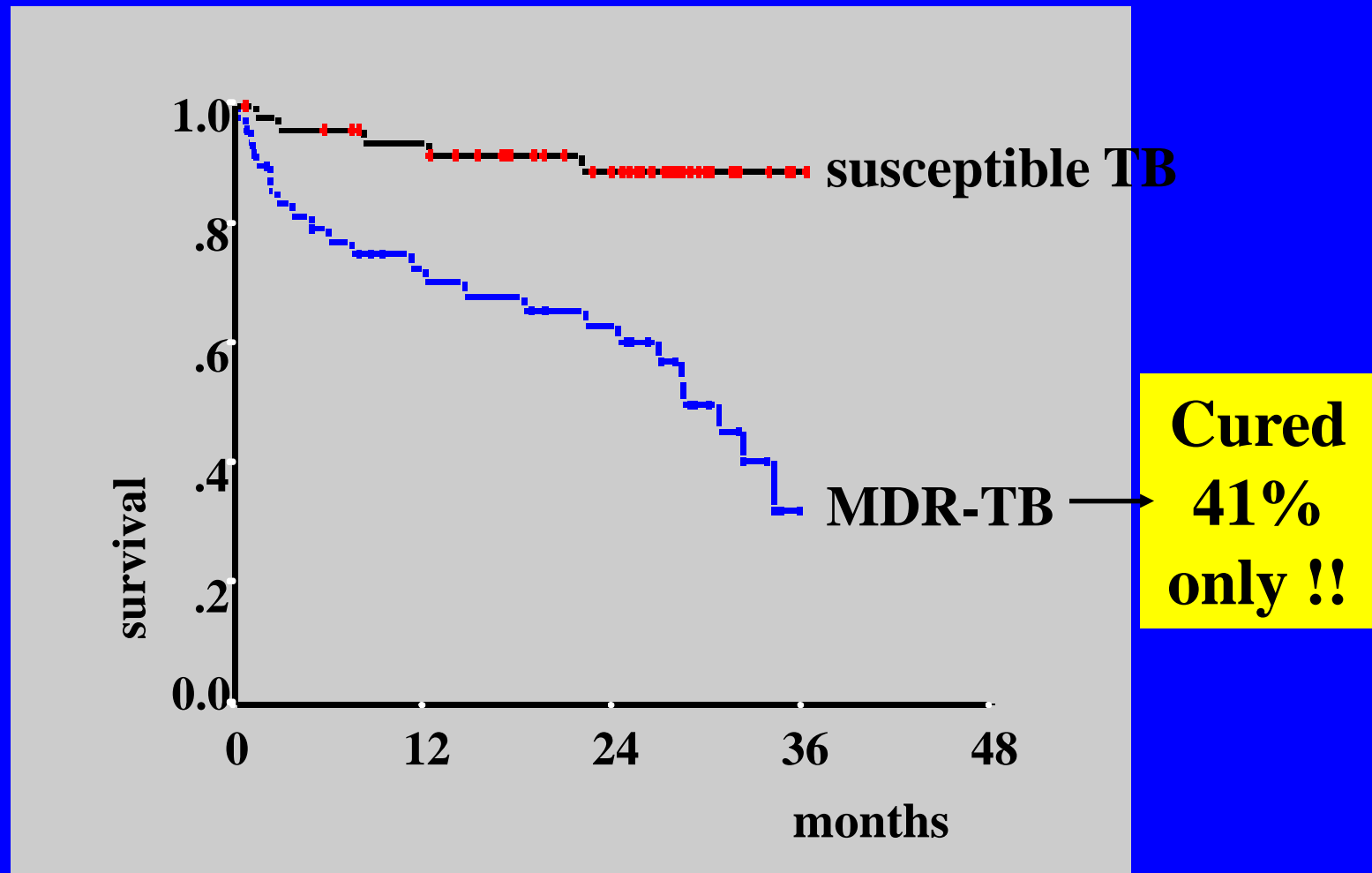
## 1st step: < 1996, no intervention

### **Outcome of Multi-drug-resistant Tuberculosis in France** A Nationwide Case-Control Study

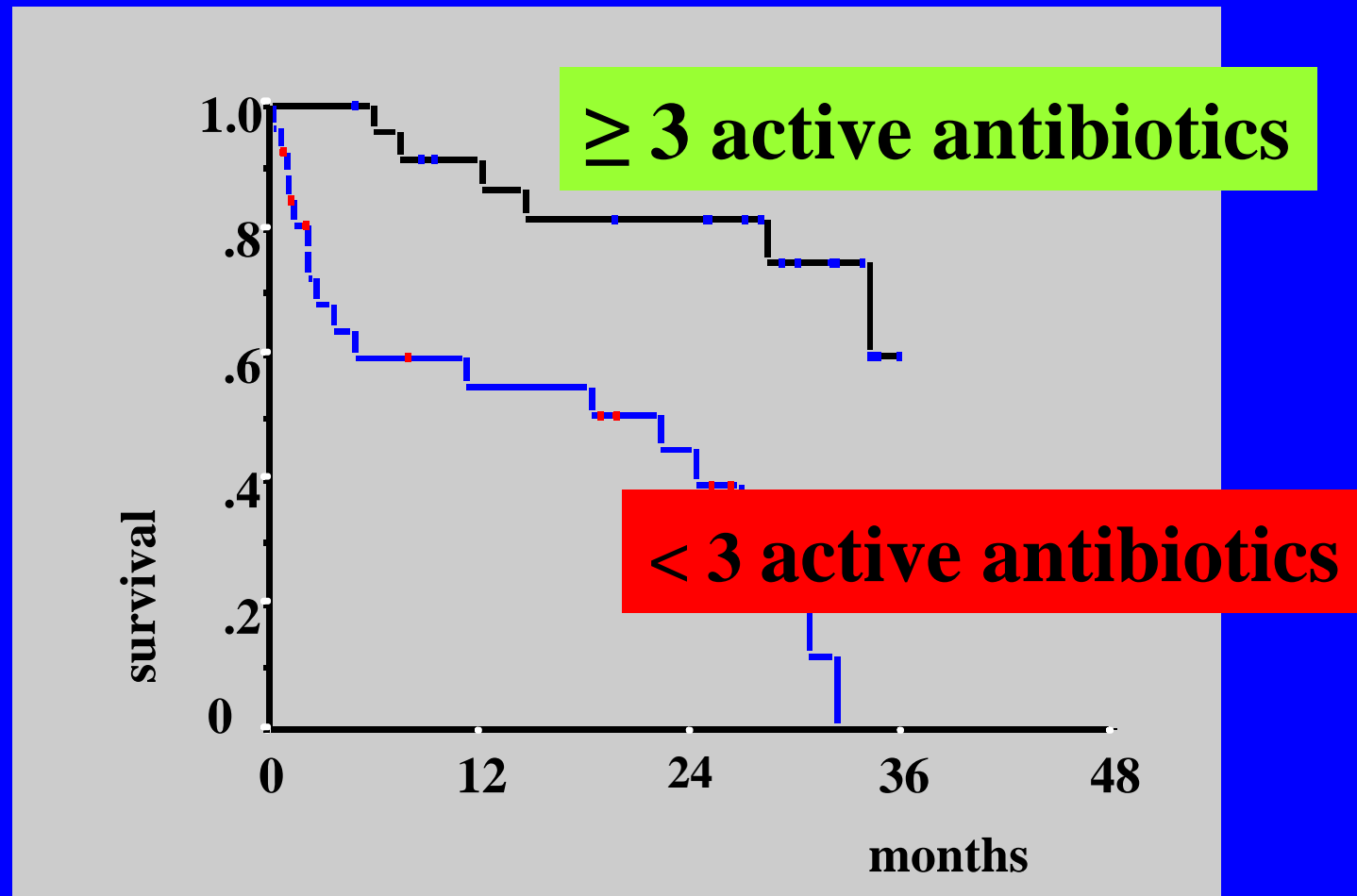
MARIE FLAMENT-SAILLOUR, JÉRÔME ROBERT, VINCENT JARLIER, and JACQUES GROSSET

**AM J RESPIR CRIT CARE MED 1999;160:587-593.**

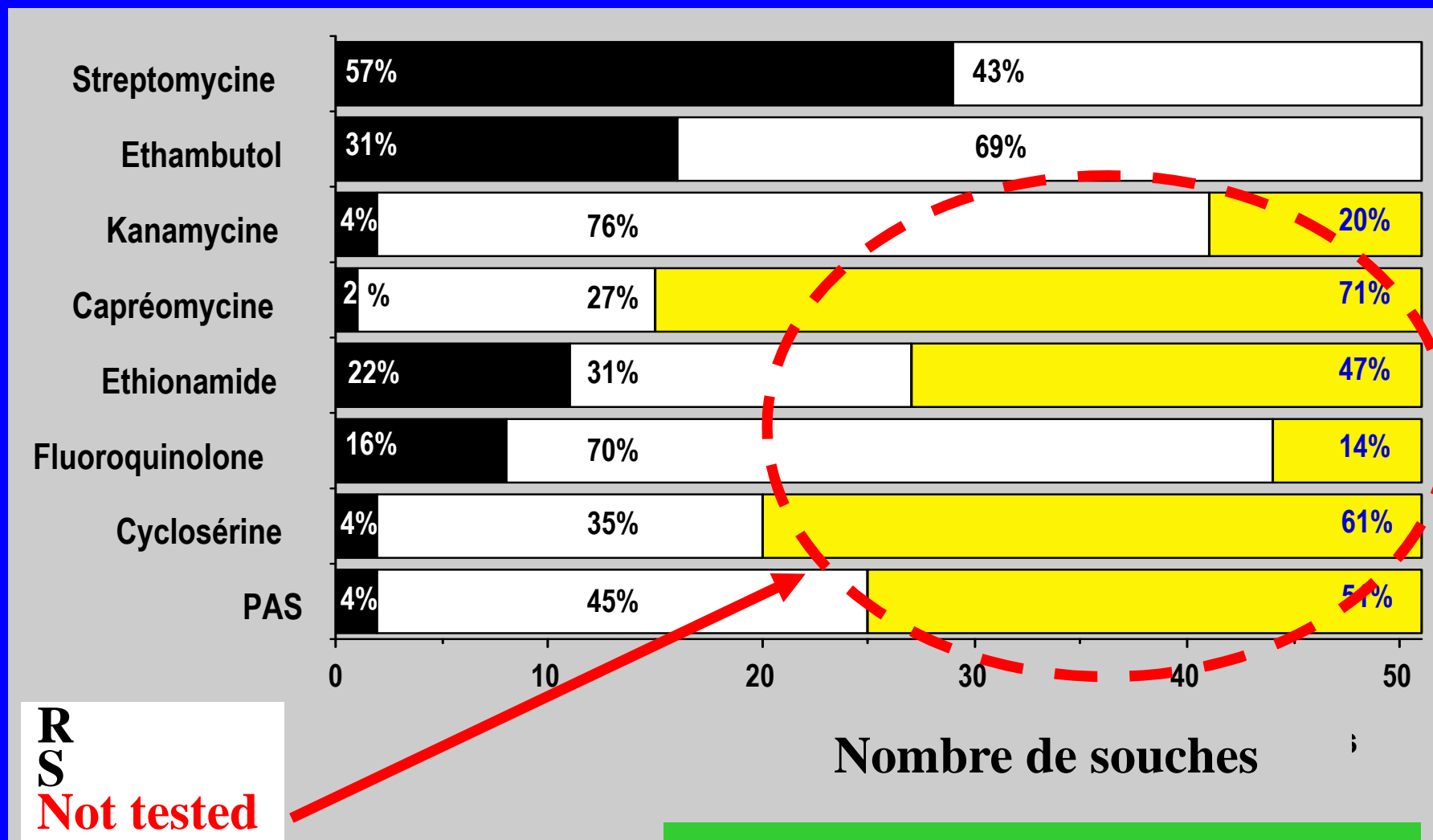
# Survival of MDR cases diagnosed in 1994 in France (n=51)



# Survival of MDR cases diagnosed in 1994 in France (n=51) depending on the number of active drugs used



# Susceptibility of strains from the 51 MDR TB cases diagnosed in 1994 in France



# **Outcome of Multi-drug-resistant Tuberculosis in France**

## **A Nationwide Case-Control Study**

MARIE FLAMENT-SAILLOUR, JÉRÔME ROBERT, VINCENT JARLIER, and JACQUES GROSSET

**AM J RESPIR CRIT CARE MED 1999;160:587-593.**

the outcome of MDR-TB in France has to be improved. A solution would be to develop a specialized unit or team for the treatment of MDR-TB, as recommended by the World Health Organization (WHO).

# TB- consilium in France

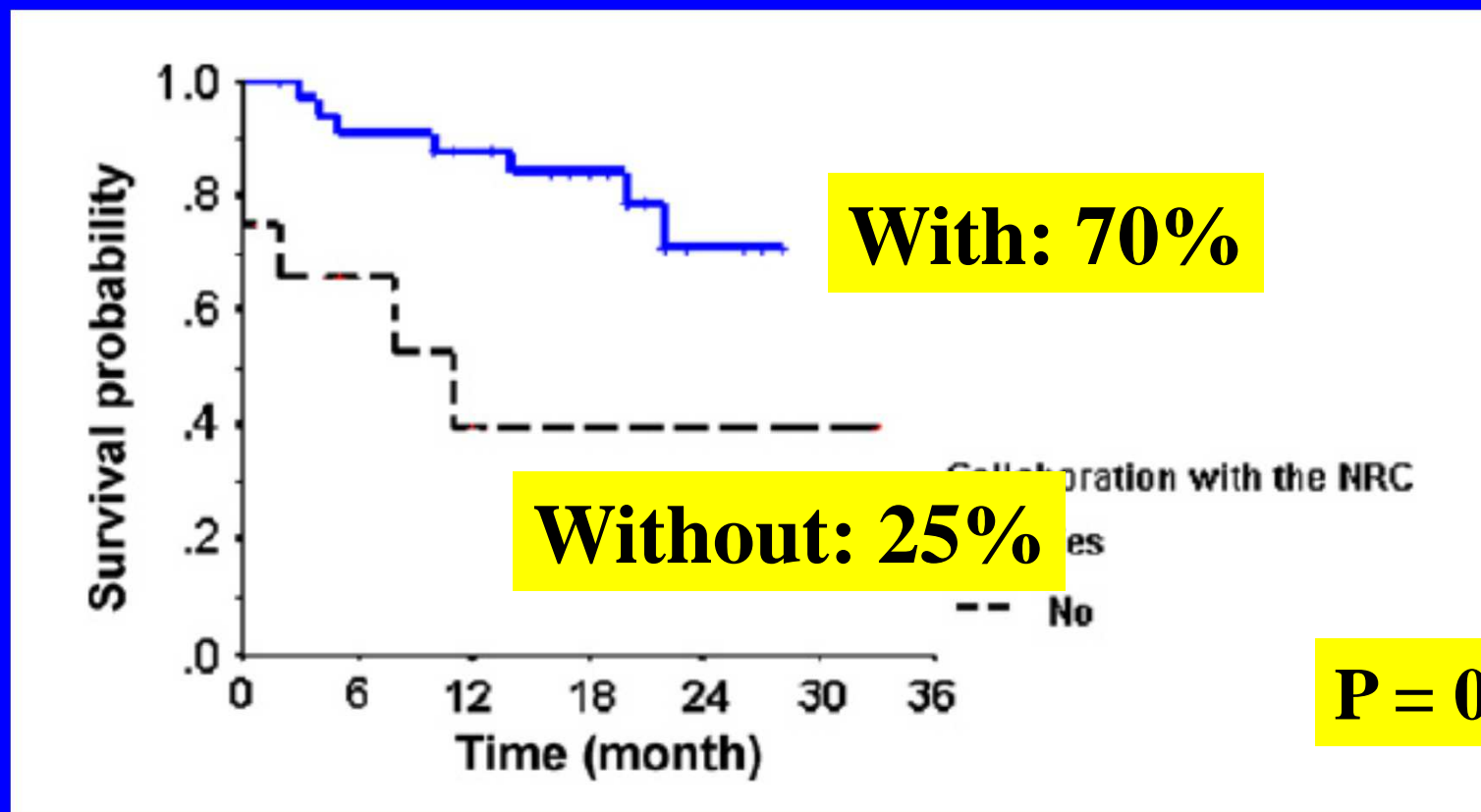
## 2nd step 1999: NRC-physician non-multidisciplinary contact

An intervention programme for the management  
of multidrug-resistant tuberculosis in France

Marie-Laure Uffredi<sup>a,b,1</sup>, Chantal Truffot-Pernot<sup>a,b</sup>, Bertrand Dautzenberg<sup>c</sup>,  
Muriel Renard<sup>b</sup>, Vincent Jarlier<sup>a,b</sup>, Jérôme Robert<sup>a,b,\*</sup>

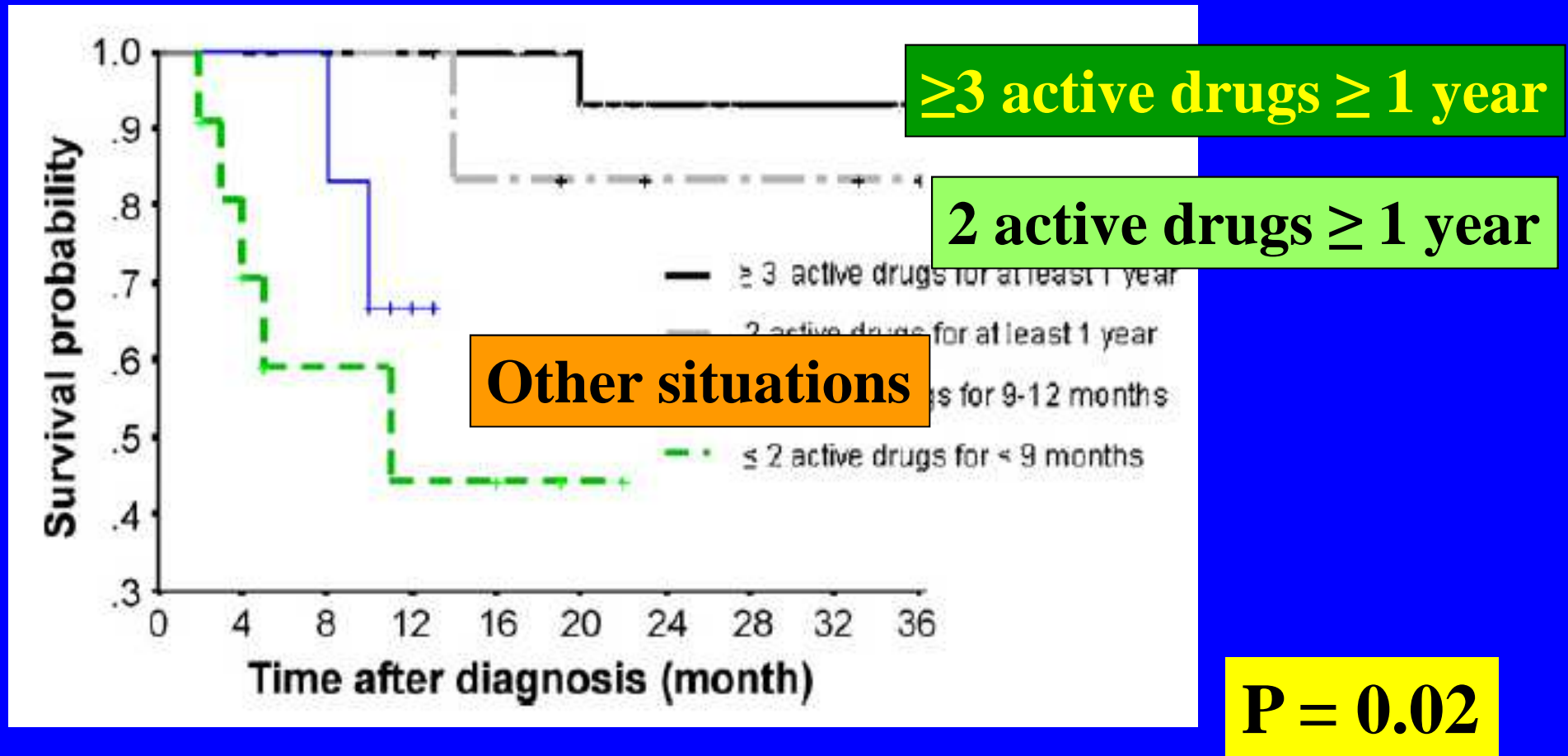
International Journal of Antimicrobial Agents 29 (2007) 434–439

# Survival of MDR cases diagnosed in 1998-99 in France (n=45) with or without the collaboration with NRC for treatment design





# Survival of MDR cases diagnosed in 1998-99 in France (n=45) depending on the number of active drugs used



# Outcome of MDR-TB in France before formal TB consillium

|  | 1994<br>(n=51)* | 1998-99<br>(n= 45)** |
|--|-----------------|----------------------|
| No of tested drugs<br>(including STR, EMB) | 5               | 8                    |
| Treatment with<br>≥ 3 active drugs         | 47%             | 84%                  |
| Overall success                            | 41%             | 67%                  |

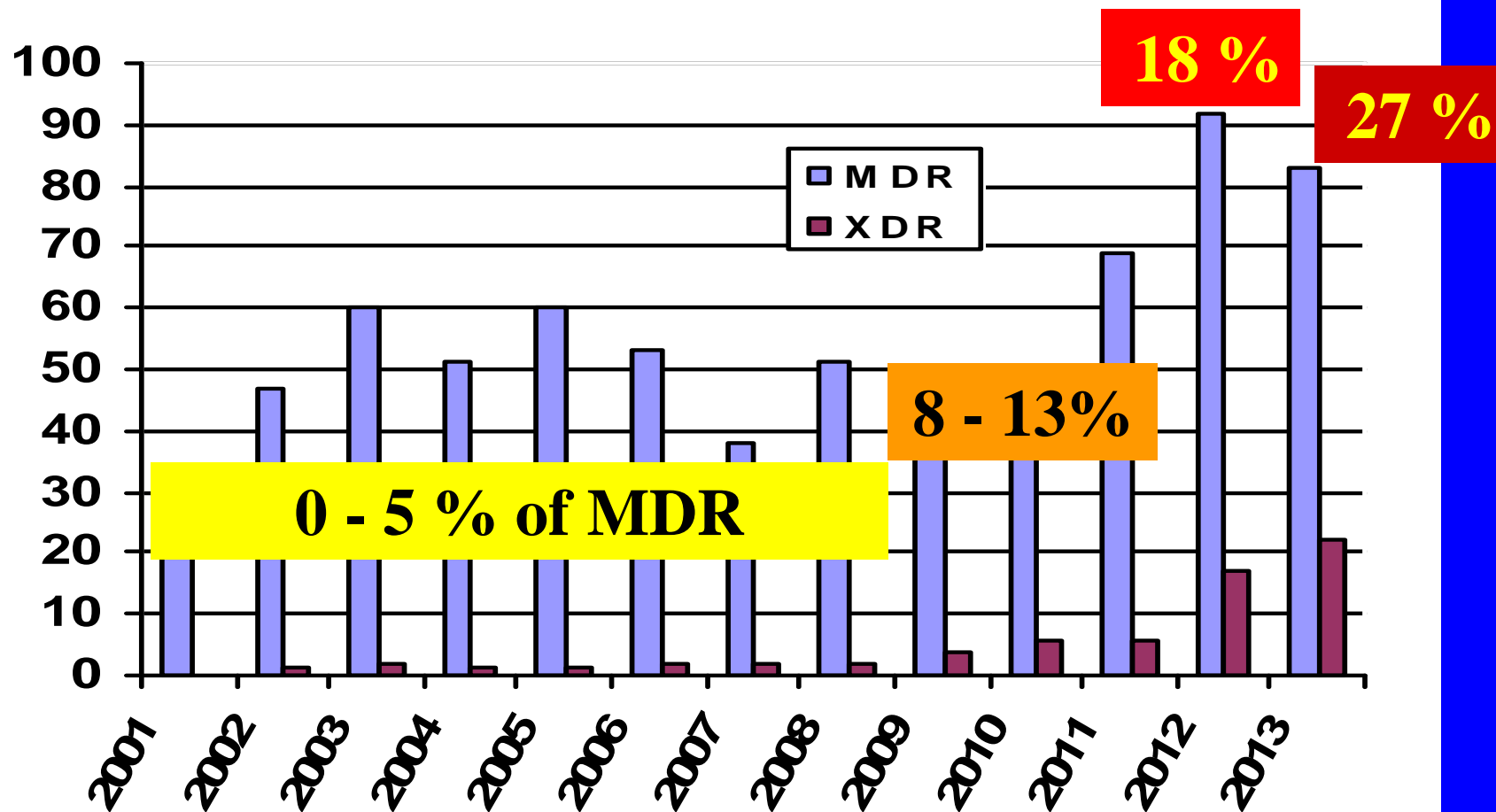
\* Saillour Am Resp Crit Care Med 1999 : non specialized teams

\*\* Uffredi Inter J Antibiot 2006 : NRC-lab/physician contact

# Needs for higher efficiency of MDR-TB treatment in France

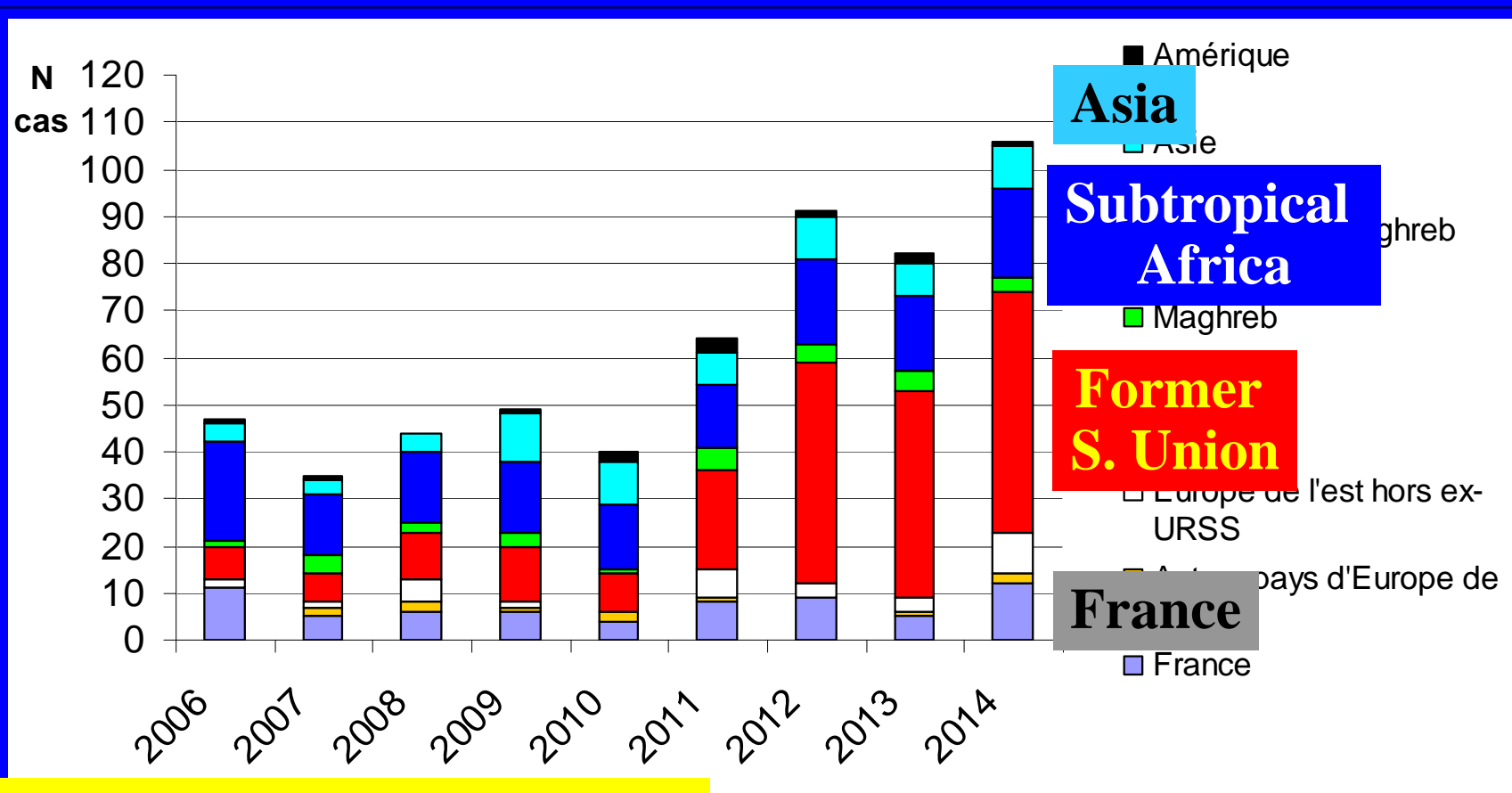


# Proportion (%) of XDR among MDR cases, France 2001-2013



<http://cnrmyctb.free.fr>

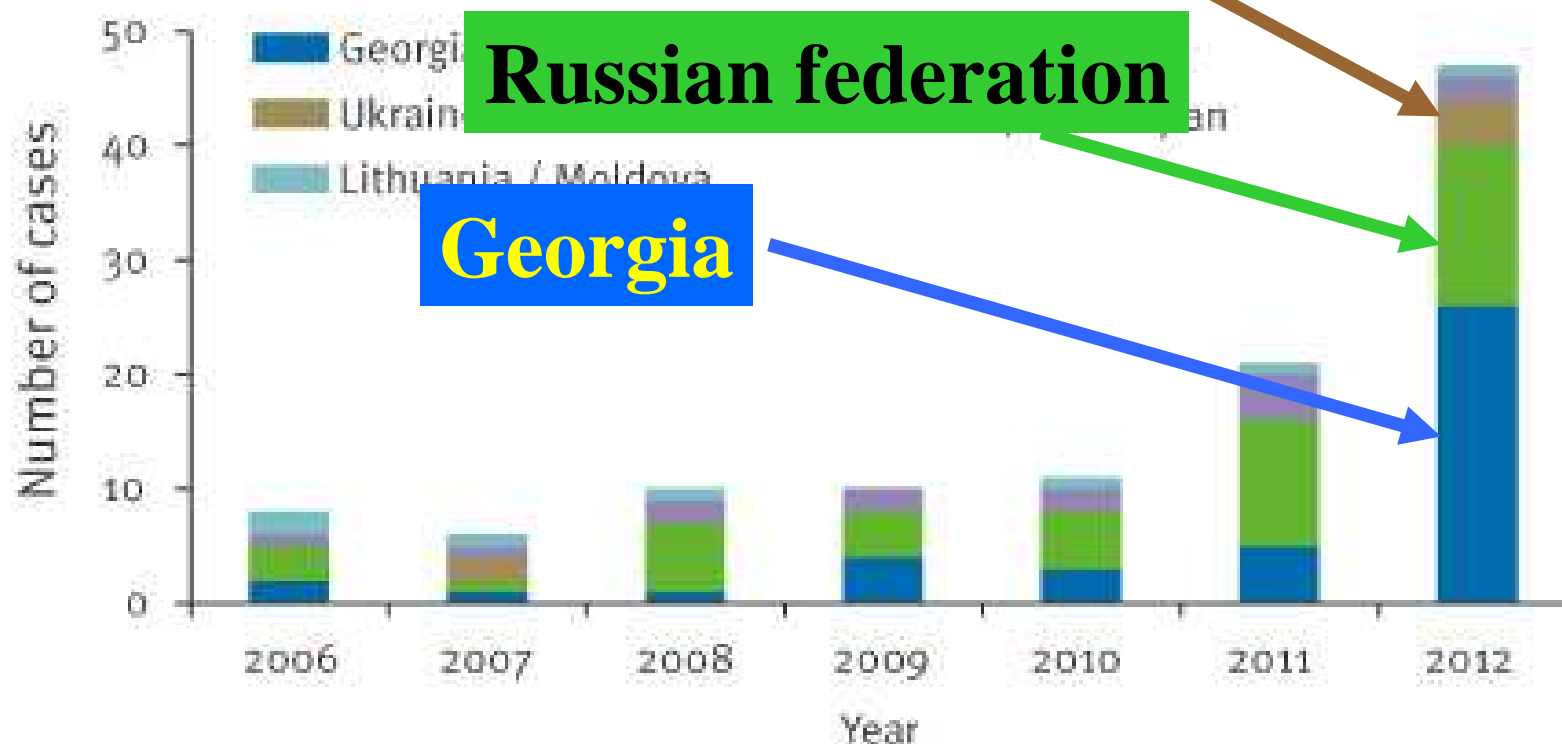
# Distribution of MDR cases by country of birth France 2006-2014



**Bernard Eurosurveillance 2013**

# Distribution MDR cases from former Soviet Union 2006-2014

multidrug-resistant tuberculosis born in the former Soviet Union, France, 2006-12



Bernard Eurosurveillance 2013

# XDR-TB cases France 2004-2014 : N. and country of birth

|      | # cases, country of birth (former SU)                       | N  |
|------|---|----|
| 2004 | 1 Algeria   | 1  |
| 2005 | 1 Mali  | 1  |
| 2006 | 1 <u>France</u> , 1 Russia                                  | 2  |
| 2007 | 1 <u>France</u> , 1 Congo                                   | 2  |
| 2008 | 1 Romania, 1 Russia   | 2  |
| 2009 | 1 Algeria, 1 Armenia, 2 Georgia                             | 4  |
| 2010 | 1 Portugal, 3 Russia, 1 Azerbaïdjan                         | 5  |
| 2011 | 1 Portugal, 2 Algeria, 1 Ivory Coast, 2 Russia              | 6  |
| 2012 | 1 Armenia, 1 Ukraine, 15 Georgia                            | 17 |
| 2013 | 1 <u>France</u> , 1 Romania, 1 Ukraine, 19 Georgia          | 22 |
| 2014 | 1 <u>France</u> , 1 Portugal, 1 Congo, 3 Russia, 20 Georgia | 26 |



# TB-consilium in France:

## 3st step 2004: consilium setting

- **Multidisciplinary team**
- **Setting up and organizer: Dr Nicolas Veziris, NRC**
  - NRC bacteriologists
  - pulmonologists
  - ID physicians
  - Pediatricians
  - Social workers
- **Working sessions at NRC (all members in the same room)**
  - Initially: 2 hours every 2 month
  - Nowadays: 4 hours every month
- **Free access, recommended by MOH but not compulsory**

# Standardized case review process

- standardized written chart, pre-filled by NRC & physician in charge
- patient origin, living places...
- TB history, **previous regimens**
- **genotypic** & **phenotypic** strain status
- discussion with the physician in charge (in room or by conference call)
- “**hand tailored**” proposed regimen
- for follow-up review: ATB dosages, side effects...
- document mailed to the physician in charge

V. Jarlier 2015

| RCP du CNR des Mycobactéries |            |                       |   | Médecin référent 1 : |   |
|------------------------------|------------|-----------------------|---|----------------------|---|
| Nom :                        | XX         | Établissement :       |   | FF                   |   |
| Prénom :                     | YY         | Service :             |   | GG                   |   |
| DN Age :                     | 01/01/1911 | Médecin référent 2 :  |   |                      |   |
| sexe :                       | M          | Établissement :       |   |                      |   |
| Type de TB :                 | pulmonaire | Service :             |   |                      |   |
| Localisation :               | LSD        | Date de première TB : |   | 2006                 |   |
| social :                     | SDF        | Ethyl/ toxico :       |   | N                    |   |
| cas relies :                 | N          |                       |   |                      |   |
| ATCD :                       | O          | HIV :                 | N | HCV :                | N |
| Pays de naissance :          | Podémie    | en France depuis :    |   | 2010                 |   |

| ANTIBIOGRAMME                      |           | Traitement |            |            |             |
|------------------------------------|-----------|------------|------------|------------|-------------|
| date prélèvement : 01/01/2014      |           | Date :     |            |            |             |
| nature prélèvement : expectoration |           | 01/01/2014 | 01/02/2014 | 01/04/2014 |             |
| INH                                | Is        |            |            |            |             |
| RIF                                | Is        |            |            |            |             |
| EMB                                | Is        |            |            |            |             |
| PZA                                | Is        |            |            |            |             |
| SM                                 | Is        |            |            |            |             |
| AMK                                | Is        |            |            |            |             |
| KAN                                | Is        |            |            |            |             |
| CAP                                | Is        |            |            |            |             |
| OF                                 | Is        |            |            |            |             |
| MXF                                | Is        |            |            |            |             |
| ETH                                | Is        |            |            |            |             |
| PAS                                | Is        |            |            |            |             |
| CYC                                | Is        |            |            |            |             |
| LNZ                                | Is        |            |            |            | neuropathie |
| TMC207                             | Is        |            |            |            |             |
| Clf                                | Is        |            |            |            |             |
| AMC/IPM                            | Is        |            |            |            |             |
| AMC/MRP                            | Is        |            |            |            |             |
| Evolution Bactrio                  | Microscop | +          | -          | -          |             |
|                                    | Culture   | +          | +          |            |             |

| 1ère RCP          |             |                       |  |
|-------------------|-------------|-----------------------|--|
| Médecins présents | date :      | Discussion / Décision |  |
| CNR               | Bligny      | Pédiatrie             | Question : neuropathie au linezolid, faut-il ajouter une autre molécule? |
| N. Veziris        | M. Jachym   | K. Chadelat           |  |
| L. Raskine        | D. Le Du    |                       |  |
| C. Bernard        |             |                       |  |
| A. Aubry          |             |                       |  |
| Pneumologie       | SAMU Social | Infectiologie         |  |
| B. Dautzenberg    | B. Riviere  | M. Jaspard            |  |
| C. Andrejak       |             |                       |  |

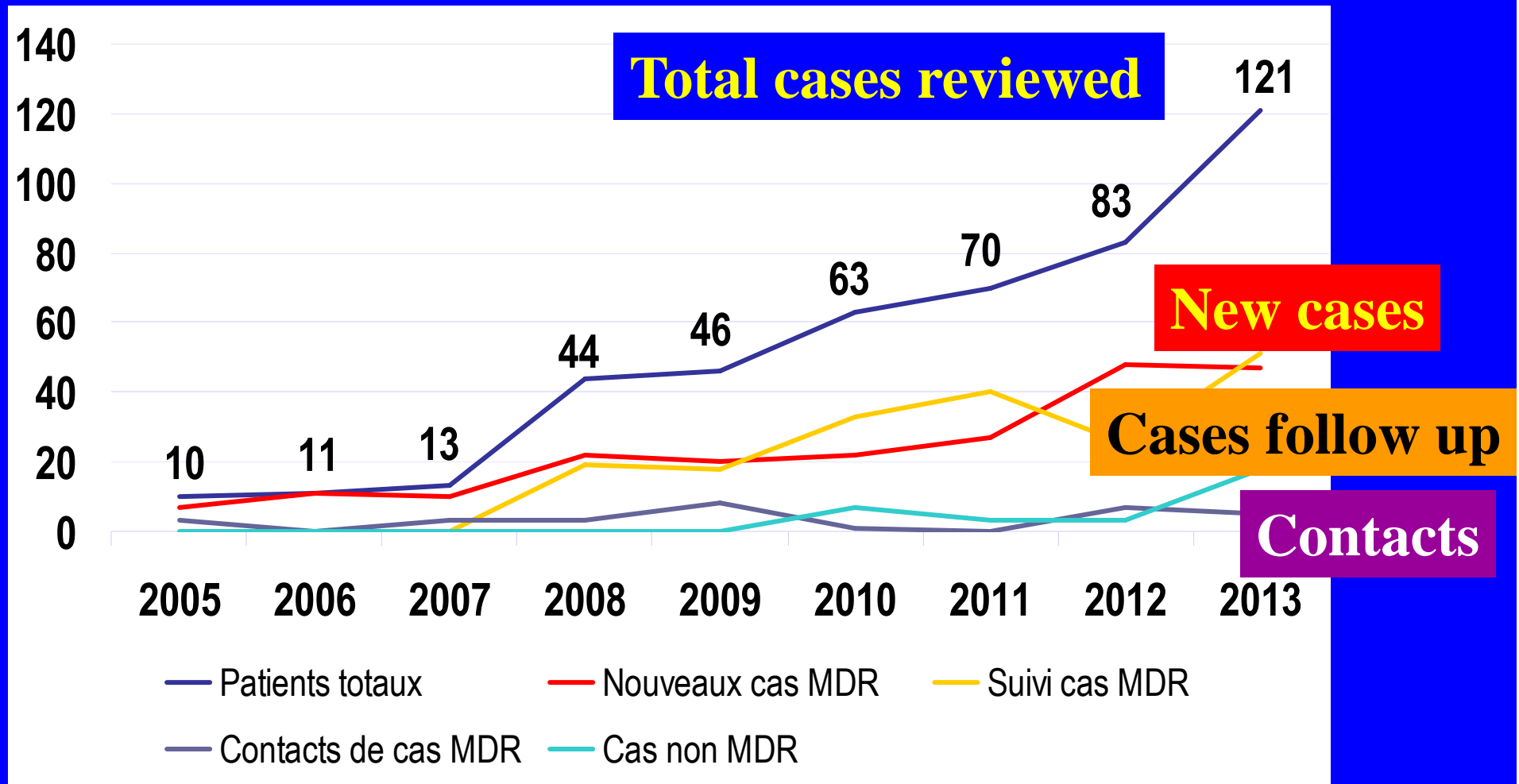
  

| RCP N°            |             |                       |  |
|-------------------|-------------|-----------------------|--|
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| CNR               | Bligny      | Pédiatrie             |  |
| N. Veziris        | M. Jachym   | K. Chadelat           |  |
| L. Raskine        | D. Le Du    |                       |  |
| C. Bernard        |             |                       |  |
| A. Aubry          |             |                       |  |
| Pneumologie       | SAMU Social | Infectiologie         |  |
| B. Dautzenberg    | B. Riviere  | M. Jaspard            |  |
| C. Andrejak       |             |                       |  |

# bacteriological data provided by NRC

- **$\geq 95$  % MDR strains received at NRC**
- **Genotype of resistance**
  - line probe assays (DNA strip):  
MTB-DR plus, MTB-DR sl
  - 12 genes sequences:  
*gyrB, pncA, ethA, ethR, atpE, eis...*
- **Phenotype of resistance**
  - 13 antibiotics
- **Genotyping for epidemiological purpose**
  - MIRU-VNTR 24 loci
  - WGS for Beijing MDR strains

# Evolution of the TB consilium activities 2005-13



# TB consilium activities 2005-13

## Number of reviews per patient

| Année de déclaration | N. réunions par patient |
|----------------------|-------------------------|
| 2005                 | 2,3                     |
| 2006                 | 2,6                     |
| 2007                 | 3,5                     |
| 2008                 | 2,2                     |
| 2009                 | 2,6                     |
| 2010                 | 2,9                     |
| 2011                 | 2,2                     |
| 2012                 | 2,8                     |
| 2013                 | 2                       |
| Total                | 2,5 (1-8)               |

**Average: 3 reviews per patient**

## TB consilium activities 2005-13: Proportion of patients reviewed & number of reviews, per type of patient

| Résistance       | N patients | % reviewed | N reviews per patient |
|------------------|------------|------------|-----------------------|
| <b>MDR*</b>      | 350        | 41 %       | 2,2                   |
| <b>Pre XDR**</b> | 108        | 55 %       | 2,8                   |
| <b>XDR</b>       | 58         | 72 %       | 3,1                   |

\* Sans résistance additionnelle aux fluoroquinolones et aux injectables de deuxième ligne

\*\* Résistance additionnelle aux fluoroquinolones ou aux injectables de

Higher exhaustivity and more reviews for pre-XDR & XDR  
than for « simple » MDR

# Evolution of outcome of MDR-TB

## France 1994-2010's

|  | 1994<br>(n=51)* | 1999<br>(n= 45)** | > 2010<br>(n > 500***) |
|--|-----------------|-------------------|------------------------|
| # tested drugs<br>(including STR, EMB) | 5               | 8                 | 13                     |
| Treatment with<br>≥ 3 active drugs     | 47%             | 84%               | ~100%                  |
| Succes                                 | 41%             | 67%               | ~80%                   |

\* Saillour Am Resp Crit Care Med 1999 : no intervention

\*\* Uffredi Inter J Antibiot 2006 : NRC-lab/physician contact

\*\*\* TB consilium

# Next step for TB-consilium in France

## **National register**

- shared by all stakeholders
- for facilitating patient management
- for measuring outcome

(project ongoing with health authorities)



**Additional information  
on MDR-TB  
provided by NRC**

# Mutations involved in isoniazid & rifampicine resistance

n = 317 MDR cases, France 2006-2012

| INH ( <i>katG</i> , <i>inhA</i> )                        | RMP ( <i>rpoB</i> ) | N   | %    |
|--|---------------------|-----|------|
| <i>katG</i> S315T alone                                  | S 531 L alone       | 149 | 47 % |
|  | S 526 alone         | 29  | 9 %  |
|  | other               | 30  | 9%   |
| other mutation <i>katG</i> alone                         | S 531 L alone       | 7   | 2 %  |
|  | other               | 11  | 3%   |
| -15 promotor <i>inhA</i> alone                           | S 531 L alone       | 28  | 9%   |
|  | other               | 4   | 1%   |
| <i>katG</i> S315T + -15 prom <i>inhA</i>                 | S 531 alone         | 16  | 5 %  |
|  | other               | 10  | 3 %  |
| other combinaisons<br><i>katG</i> + promotor <i>inhA</i> | S 531L alone        | 13  | 4%   |
| No mutation  | S 531 L or other    | 9   | 3%   |
| <i>katG</i> S 315 T or -15 <i>inhA</i>                   | no mutation         | 3   | 1%   |

**Total yellow = 3/4**

KatG = INH activator, InhA = INH target

# Phylogeography of MDR cases in France

## 98 MDR strains isolated in France (2009-2010)

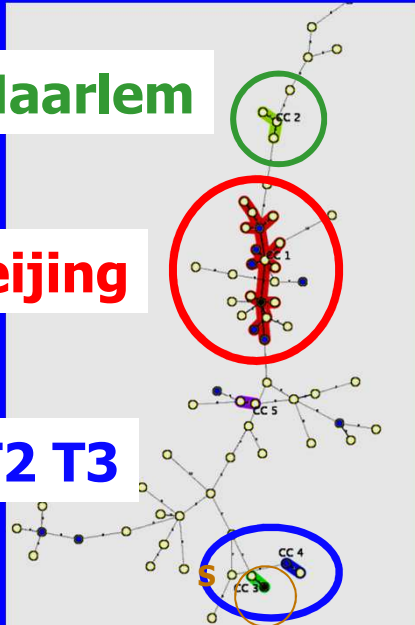
### analysis by spoligotyping, RFLP + MIRU-VNTR 24

### Distribution by country of birth

**Haarlem**

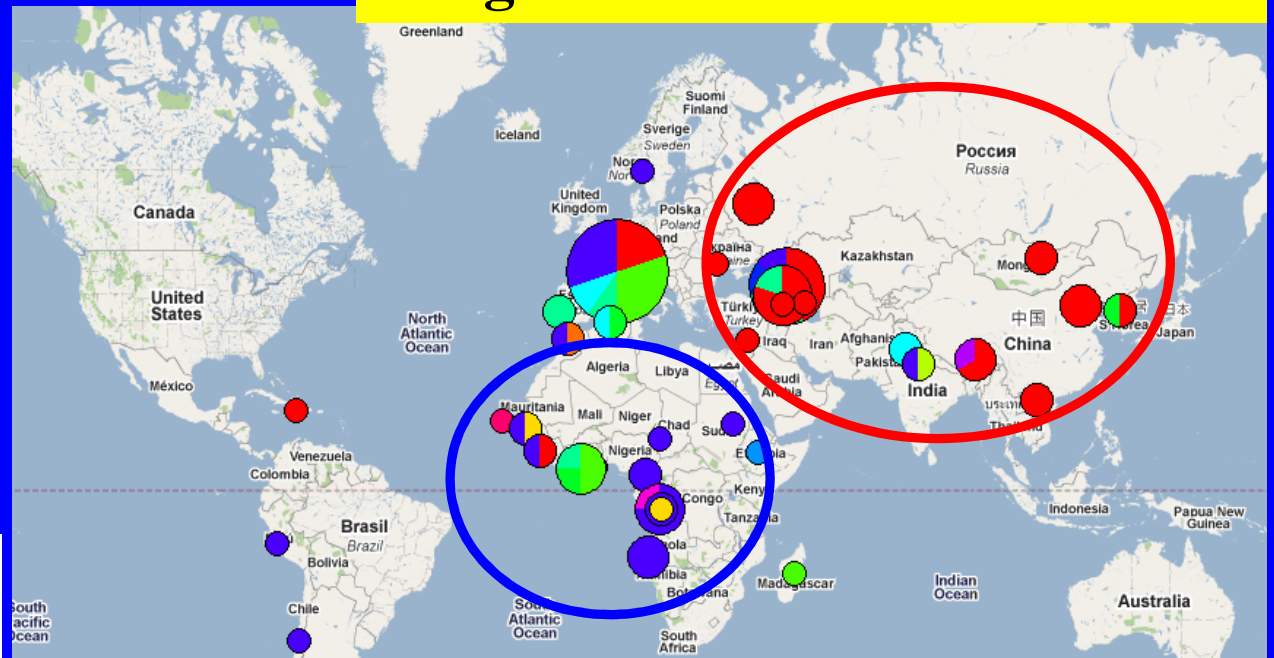
**Beijing**

**T1 T2 T3**



- 5 clonal complexes
- 13 clusters (41% of cases)
- Beijing (red):
  - 6 clusters
  - 20% of cases
  - differentiated by RFLP

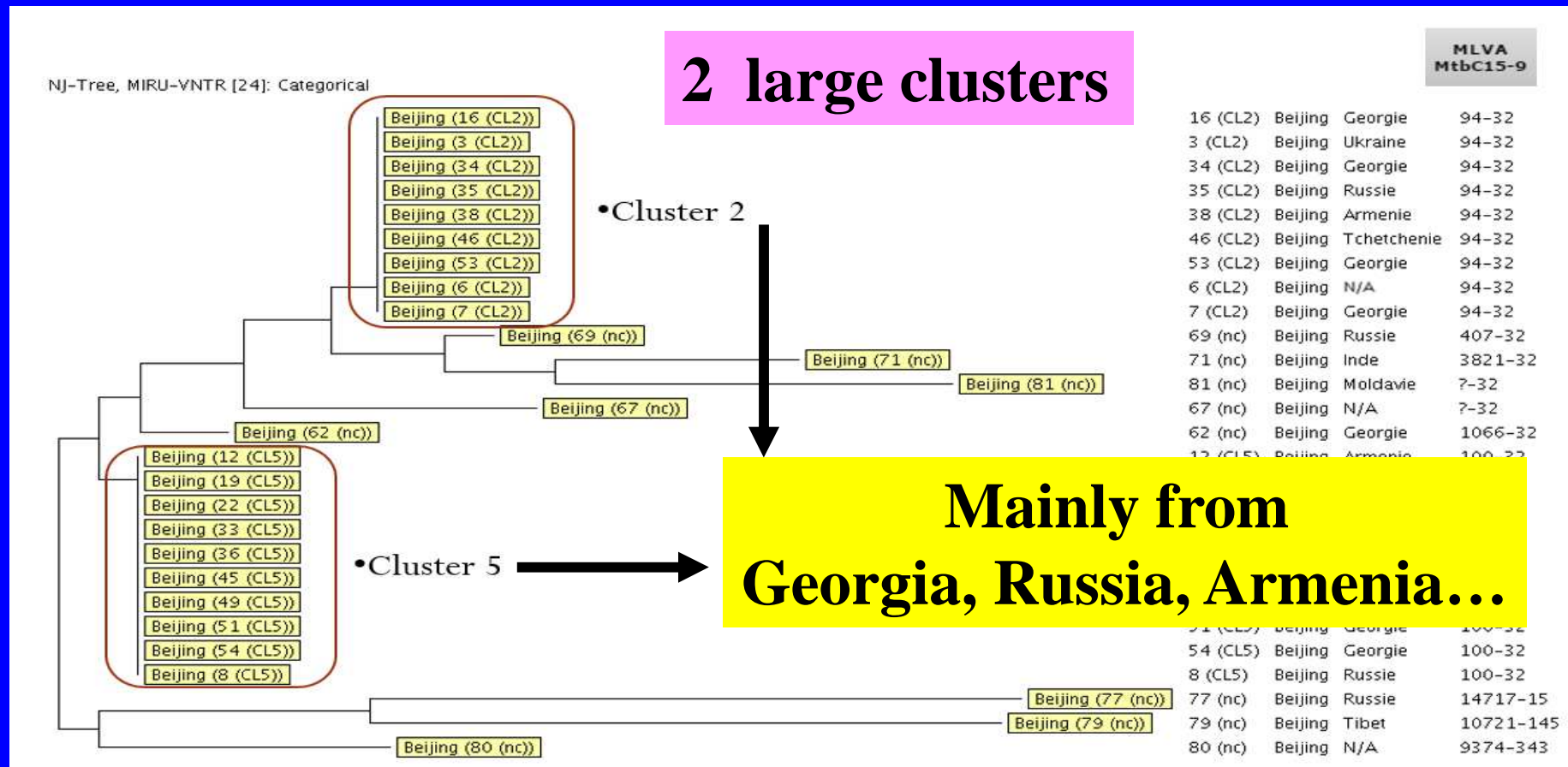
**Sougakoff Clin Microb Inf 2011**



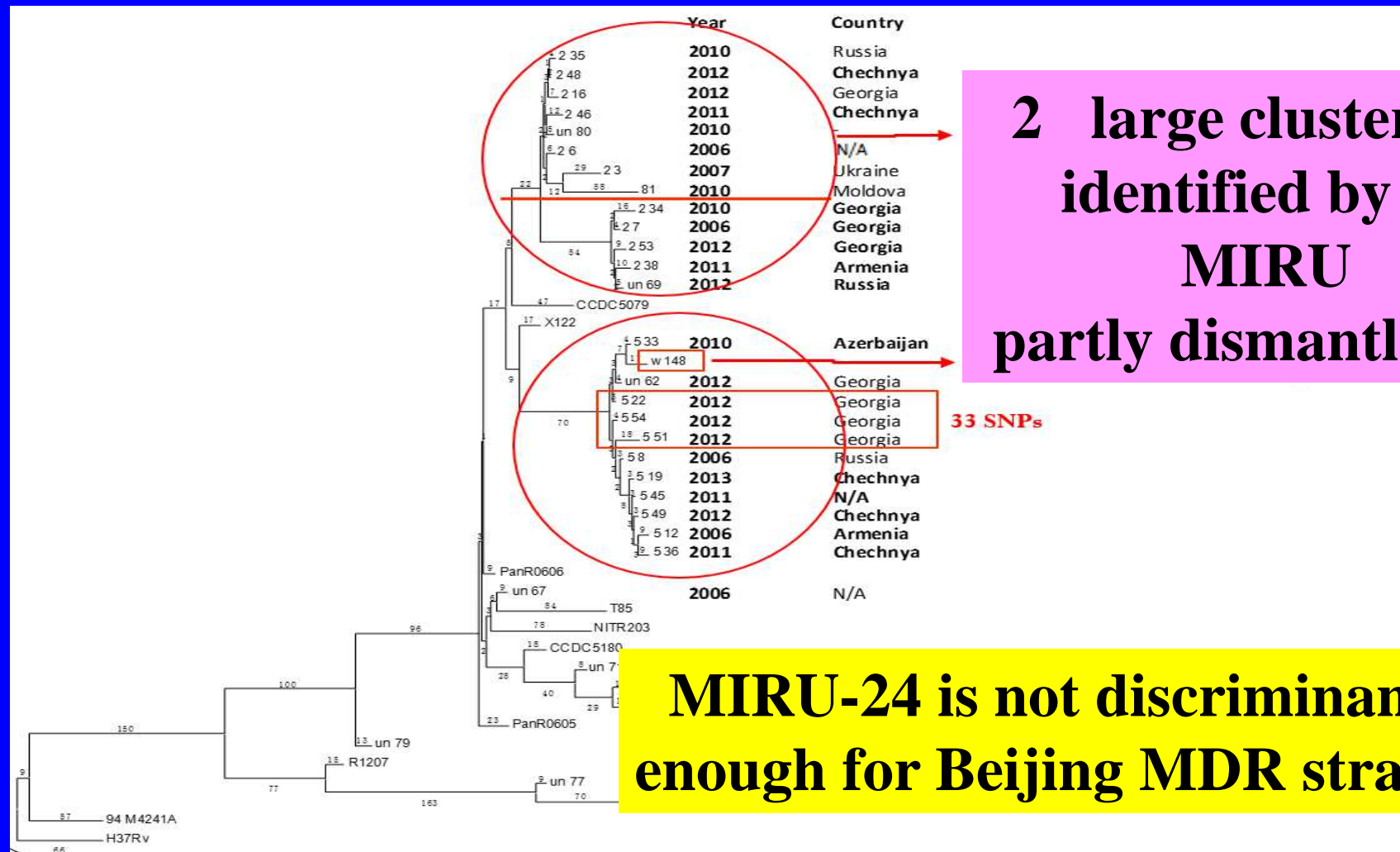
**dark blue:T   red:Beijing   green:Haarlem-LAM**  
**orange:Cameroon   light blue: S**  
**Kaki:Dehli**

- **Africa born : 52% T**
- **Eastern Europe & Asia born: 75% Beijing**

# Clustering among 27 MDR Beijing strains based on MIRU-VNTR (24 loci)



# Clustering among the same 27 MDR Beijing strains based on WGS



2 large clusters  
identified by  
MIRU  
partly dismantled

33 SNPs

MIRU-24 is not discriminant  
enough for Beijing MDR strains



March 24th 1882  
announcement of  
TB bacillus discovery  
by Robert Koch

<http://cnrmmyctb.free.fr>