Situation of global resistance in the region

WHO CC UPDATES

WHO Collaborating Centre
for surveillance of antimalarial drug resistance

- Lise MUSSET

- 14th November 2018

POUR LA RECHERCHE, POUR LA SANTÉ,
POUR DEMAIN

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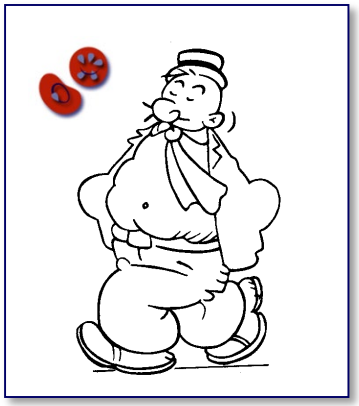
1.1 Methods to evaluate resistance



Parasites

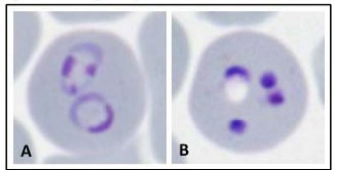
Patient

Therapeutic efficacy studies

- Adequate therapeutic response
- Therapeutic failures

In vitro tests

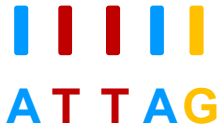
- Inhibitory concentration 50% (IC_{50})
- Survival rates



Molecular methods

- Mutations

Sensitive



Resistant

- Gene amplification and/or expression

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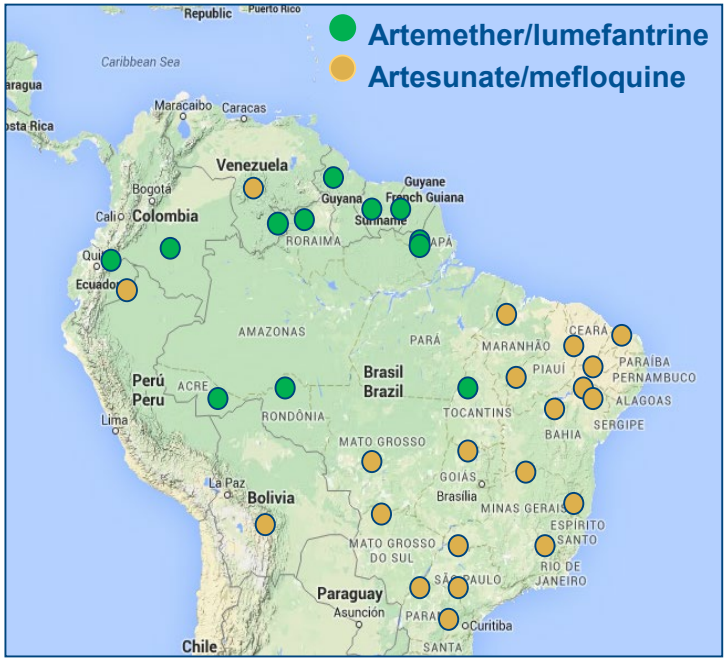
1.2 Recommended treatment in the region

P. falciparum

- **Chloroquine**
- **AR-Lumefantrine:** Coartem®, Riamet®
- **AS-Mefloquine**



P. vivax

- **Chloroquine**
- **Primaquine**

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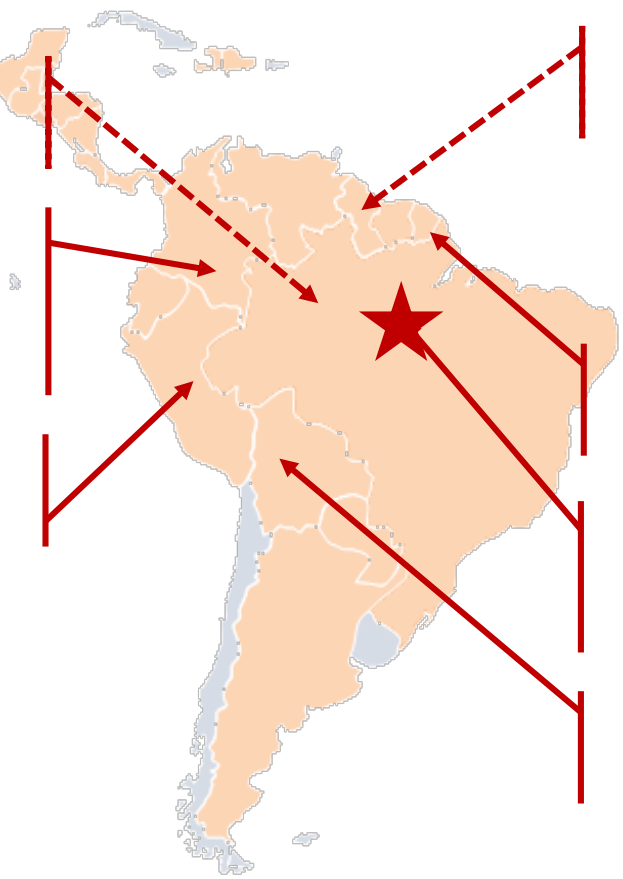
2.1 *P. vivax* resistance to chloroquine

In vivo response	*In vitro* phenotyping	Molecular marker
On Day 28	IC_{50} > 100nM Very difficult	Unknown *pvcrt-o?* *pvmdr1?*

Brésil :
1997: CQ, 1 cas

Colombie :
2001: CQ, 11% (n=3/27)
2007: CQ, 9% (n=2/22)

Pérou :
1998-2001: CQ, 1,1% (n=2/177)



Guyana :
1996*: CQ, **3 cas**

Brésil : Oiapoque
2011: CQ+PQ, 1,1% (n=1/95)

Brésil : Manaus
2004-05: CQ, 10,1% (n=11/109)
2007-08: CQ+PQ, 5,2% (n=7/135)

Bolivie :
2011: CQ+PQ, **6,5%** (n=6/96)

Report cases
Clinical trials
No *vivax* transmission
Endemic for *vivax*

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3.1 *P. falciparum* resistance to chloroquine

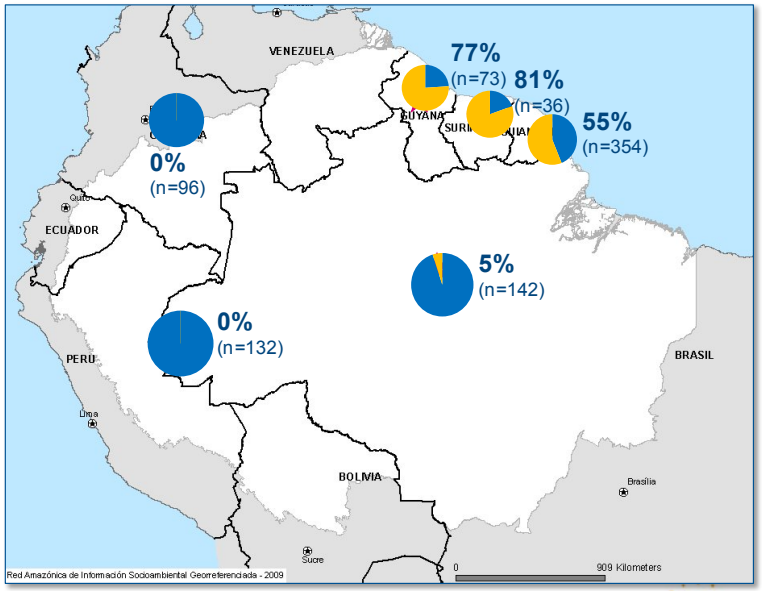
In vivo response	*In vitro* phenotyping	Molecular marker : *pfcrt*
On Day 28	IC_{50} > 100nM	K76T = Resistant K76 = Susceptible K76T + C350R = Susceptible

Meso America (Haiti, Nicaragua)

- Chloroquino-susceptible parasites

Amazonia

- Chloroquino-resistant parasites
- Presence of susceptibles on the Guiana Shield (C350R)



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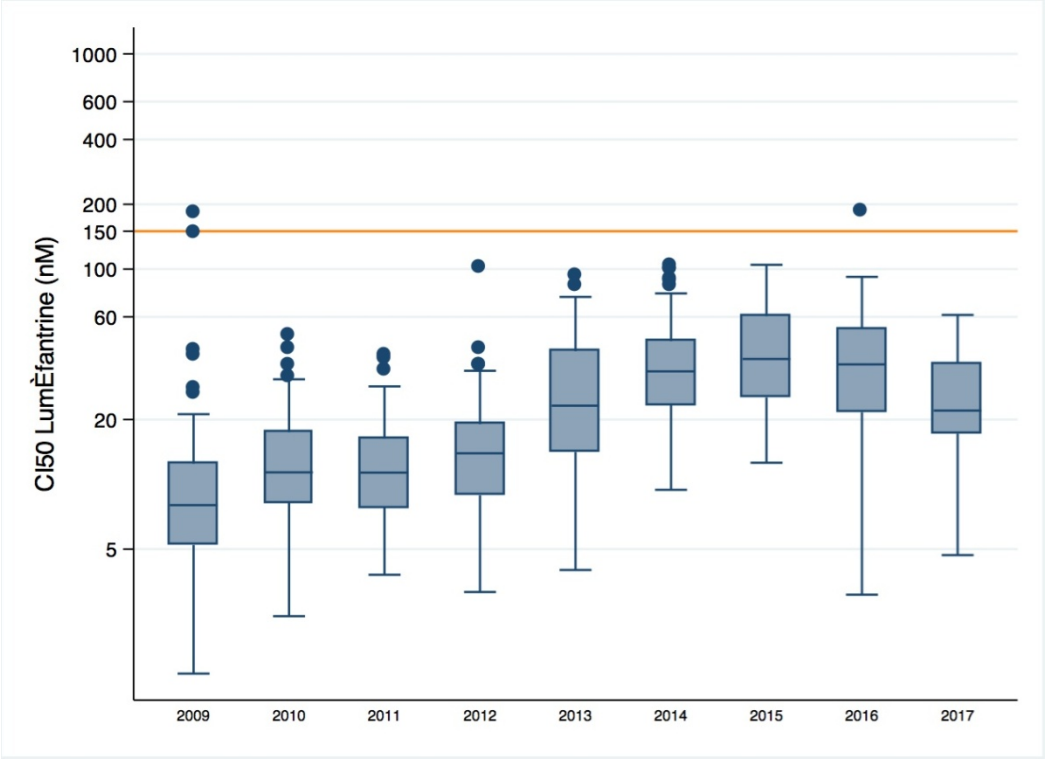
3.2 *P. falciparum* resistance to lumefantrine

In vivo response	*In vitro* phenotyping	Molecular marker : *pfcrt*
On Day 28	IC_{50} > 150nM	*pfmdr1*?

South America: Absence of resistance



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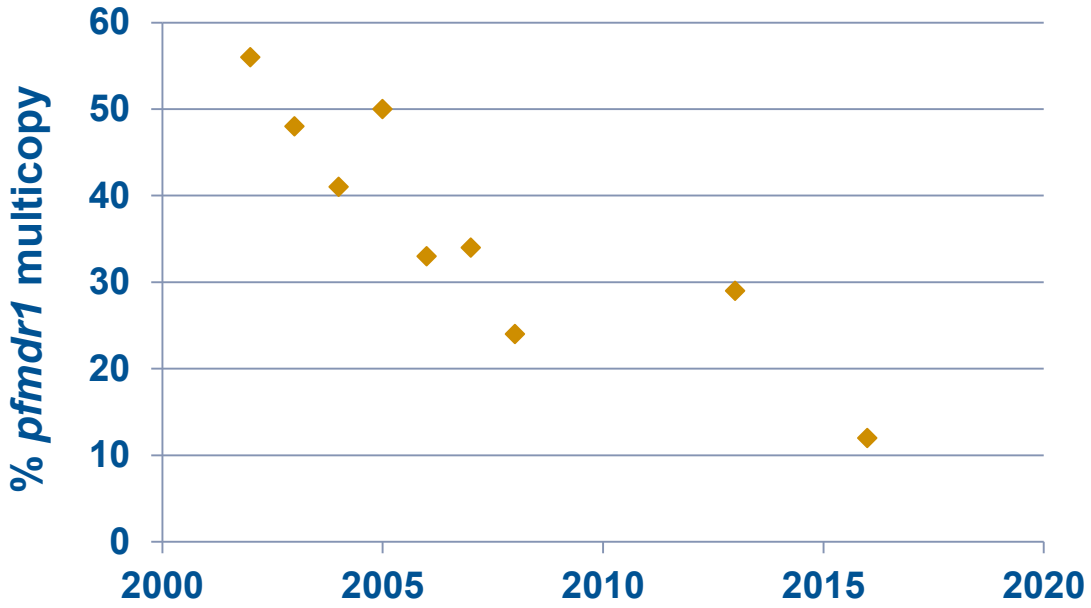
3.3 *P. falciparum* resistance to mefloquine

In vivo response	*In vitro* phenotyping	Molecular marker
On Day 28	IC_{50} > 30nM	*pfmdr1* amplification

Amazonia: Decrease of resistance



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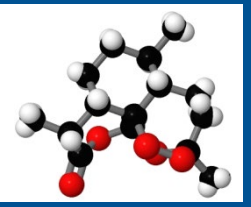
3.4 *P. falciparum* resistance to artemisinins



Parasite clearance time	*In vitro* phenotyping : RSA	Molecular marker : *pfK13*
PCT > 5h or Positive parasitemia on D3	Survival rate > 1%	Confirmed *pfk13* positions 493 - 539 - 543 - 580

HAITI
2015: No mutant (0/88)
2017: No mutant (0/77)

GUYANA
2010: cinq *pfk13* C580Y (5/99)

VENEZUELA
2013-2014: No mutant (0/41)

SURINAME
2013-2014: No mutant (0/41)

COLOMBIA
>2010: n= 523 No mutant

FRENCH GUIANA
2009-2017: n=607 ⇨ n=1 M671I

PERU
>2010: n= 69 No mutant

MANAUS
2014: n= 130 ⇨ n=1 A481V
2015: n= 63 ⇨ n=1 P475S
n=1 P553S

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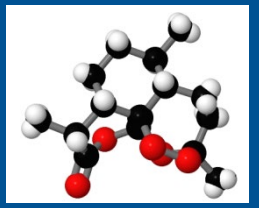
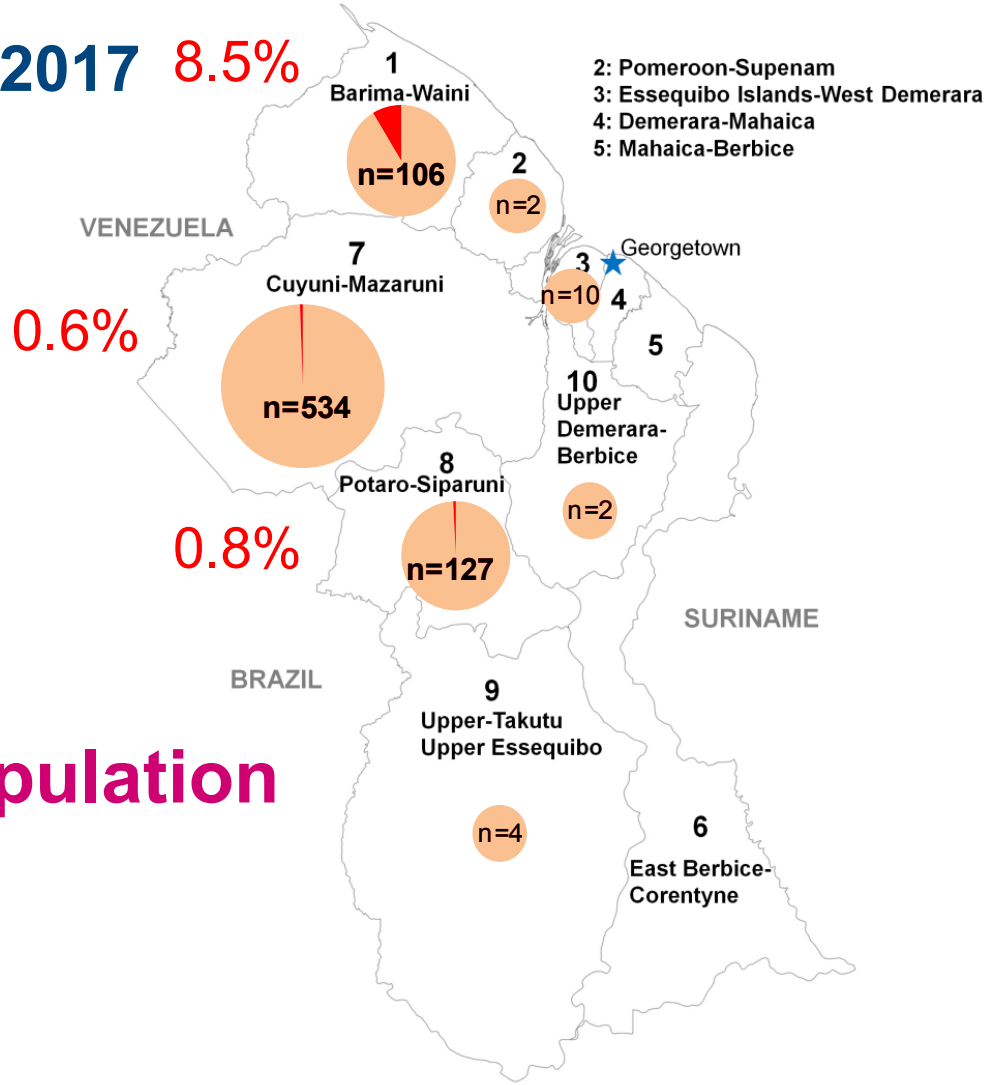
3.5 A critical situation in Guyana (1/5)



- 785 isolates 2016-2017



→ 1.7% general population

→ Mainly Region 1

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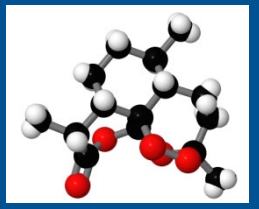
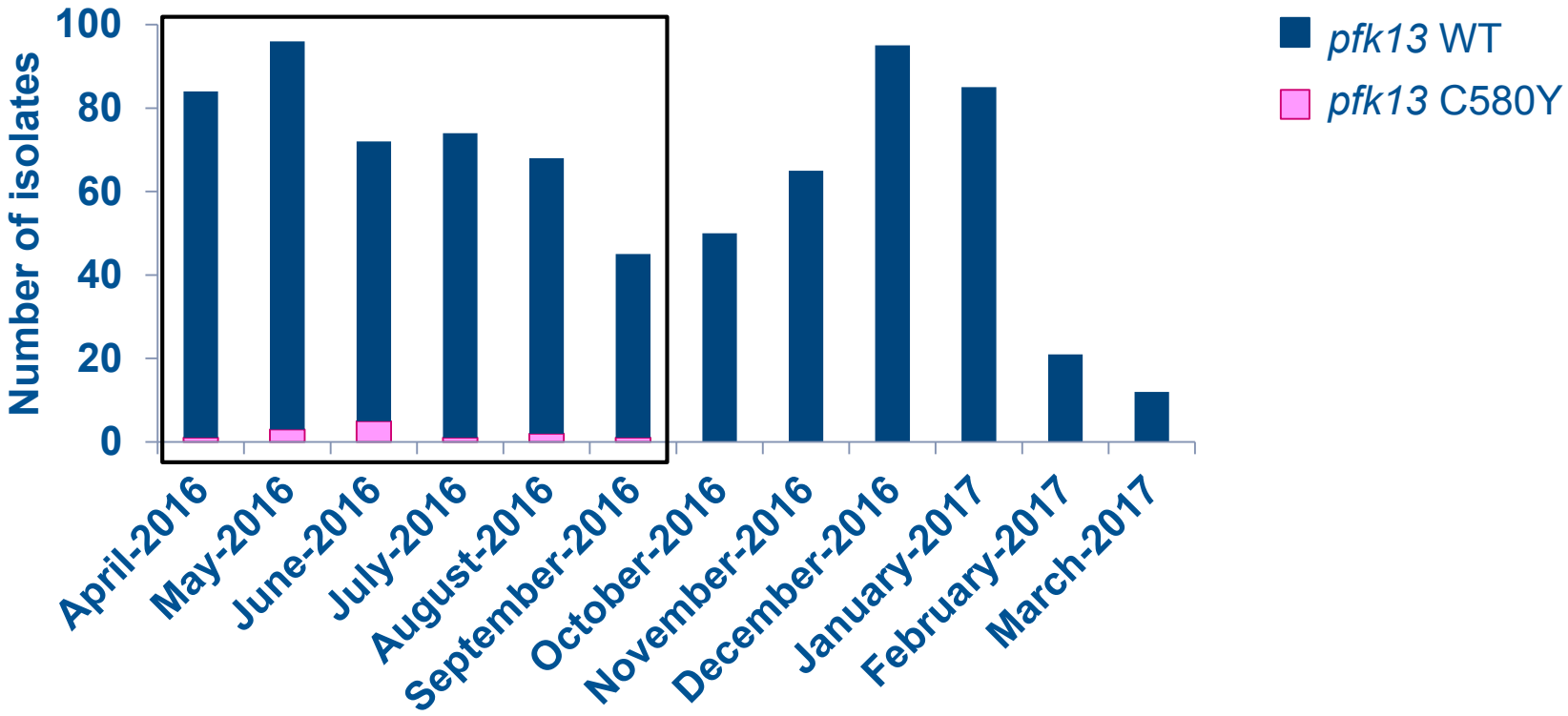
3.5 A critical situation in Guyana (2/5)



The temporal distribution



→ **Temporary transmission**

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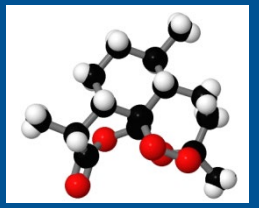
3.5 A critical situation in Guyana (3/5)



Parasite clearance time	*In vitro* phenotyping : RSA	Molecular marker : *pfK13*
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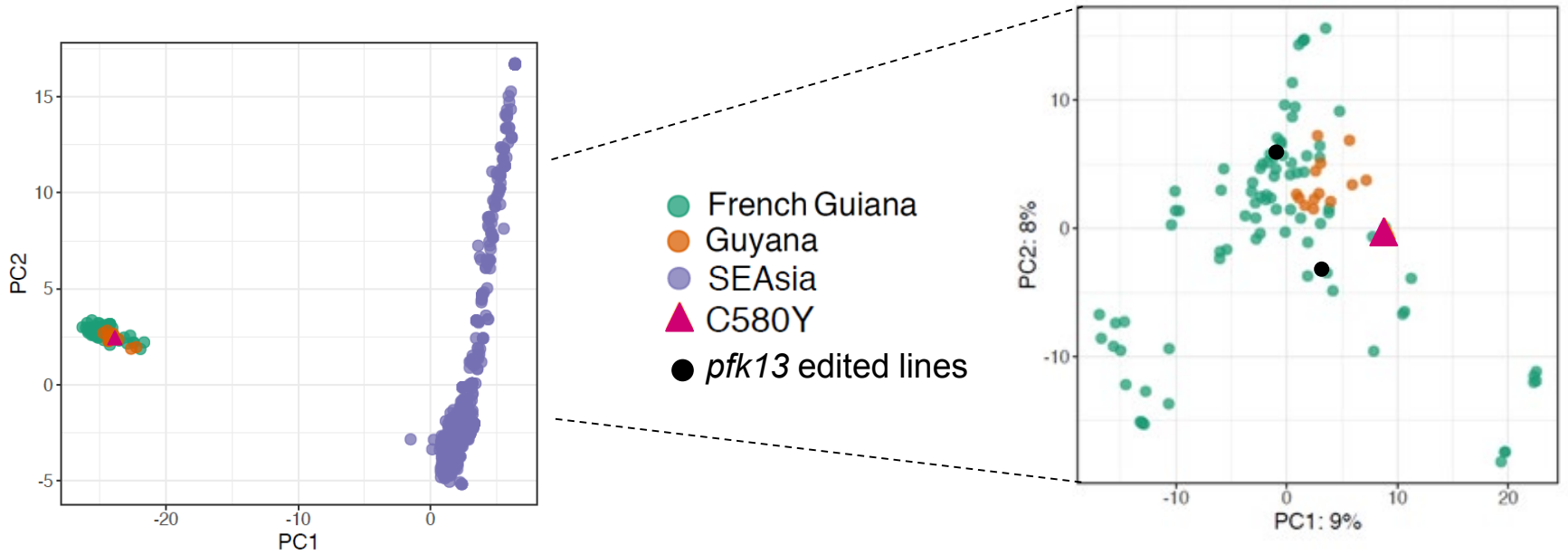
Emergence different from SouthEast Asia



→ **Clonal circulation**

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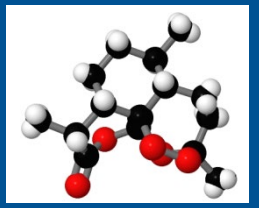
3.5 A critical situation in Guyana (4/5)



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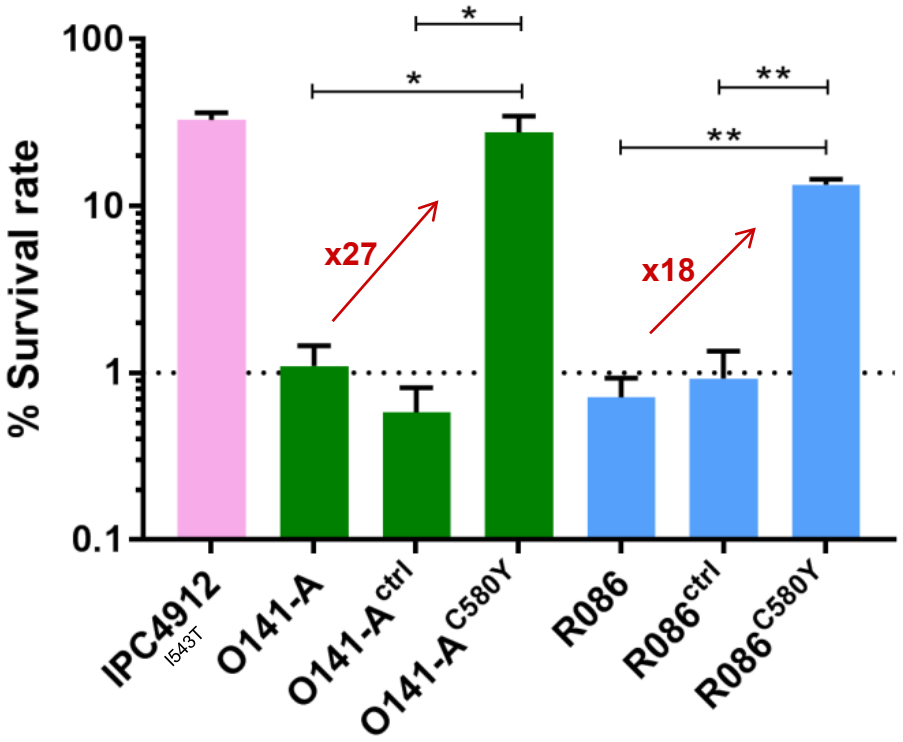

→ *In vitro* artemisinin resistance

→ Impact on AR/LU efficacy?

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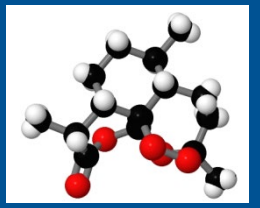
3.5 A critical situation in Guyana (5/5)



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- Country status according to WHO definition

→ **Suspected artemisinin resistance**

→ **Impact on AR/LU efficacy need to be defined**

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4.1 Discussion and perspectives

Amazonia really a hotspot for selection of resistance

- **Chloroquine**: Late 50's
- **Sulfadoxine-pyrimethamine**: Late 70's
- **Artemisinin**: Around 2010, 2008 in Cambodia

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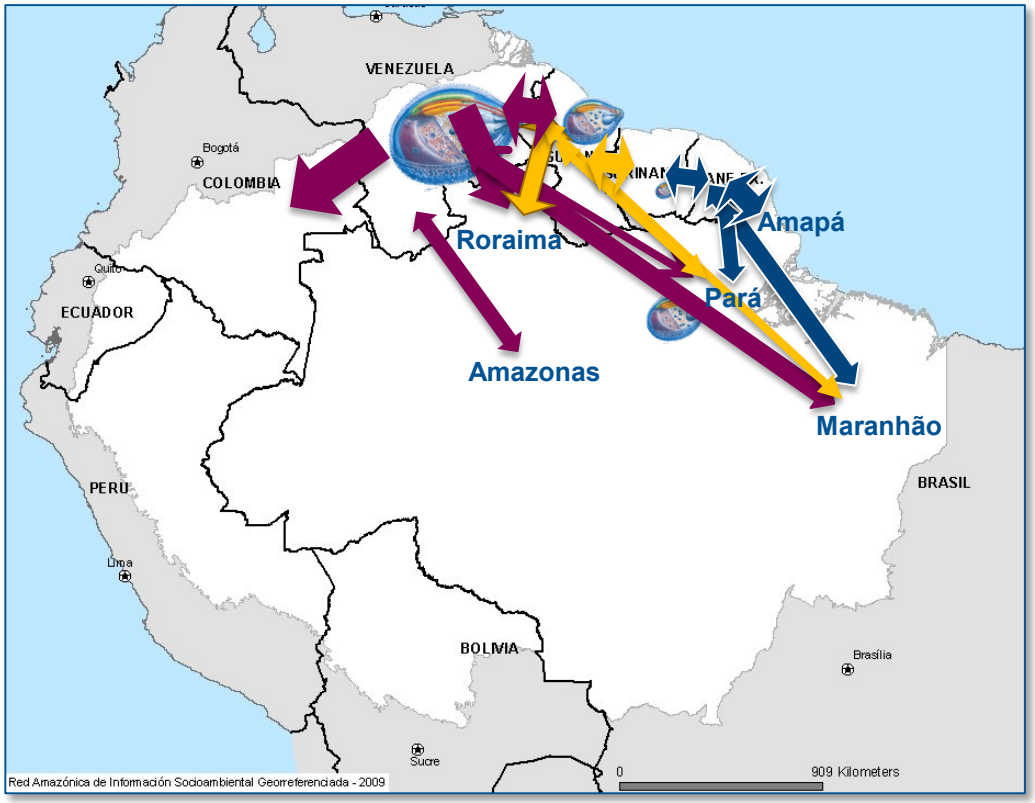
4.2 Discussion and perspectives

- Recommended antimalarial drugs still efficient
- Regarding the Guiana Shield context



Source: Heemskerk, 2014

- 30% *falciparum*
- Heterogeneity of transmission
- Transborder context
- Low population density
- Mobile populations

➢ **Strong and concerted responses are needed**

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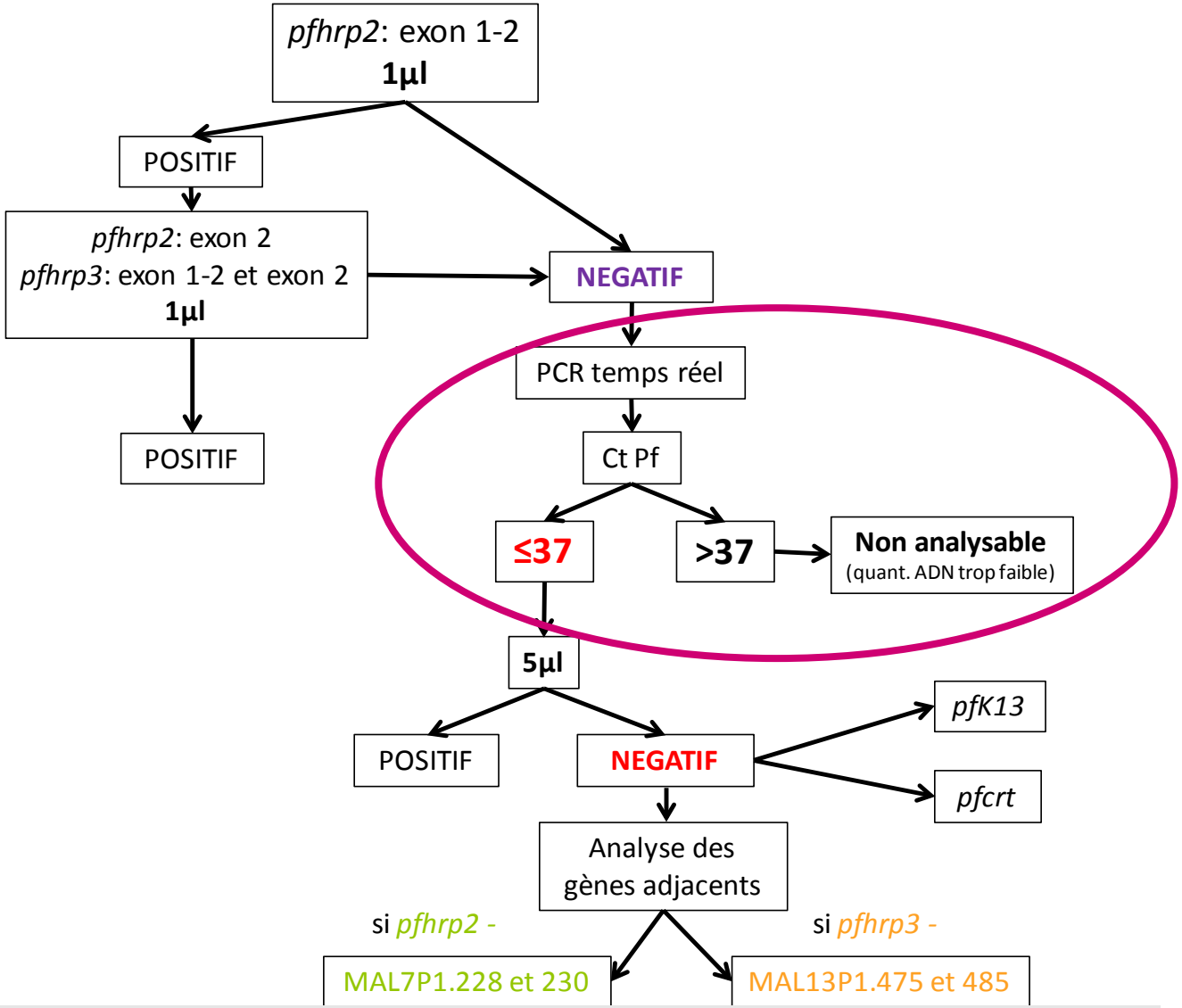
0.1 A robust method to avoid false negative



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0.2 *pfhrp2* deletion in Guyana and French Guiana

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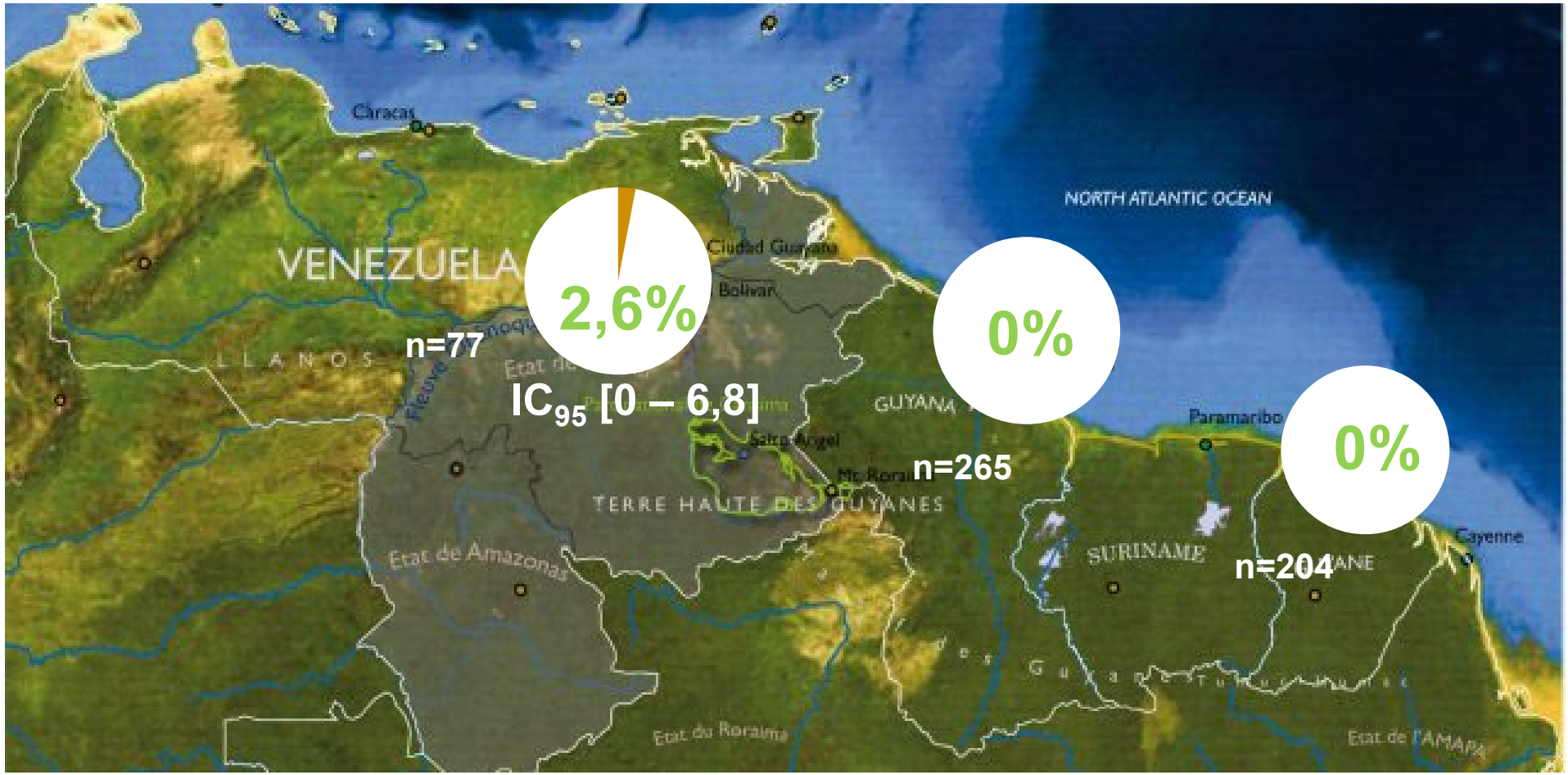
0.3 *pfhrp2* deletion in Venezuela



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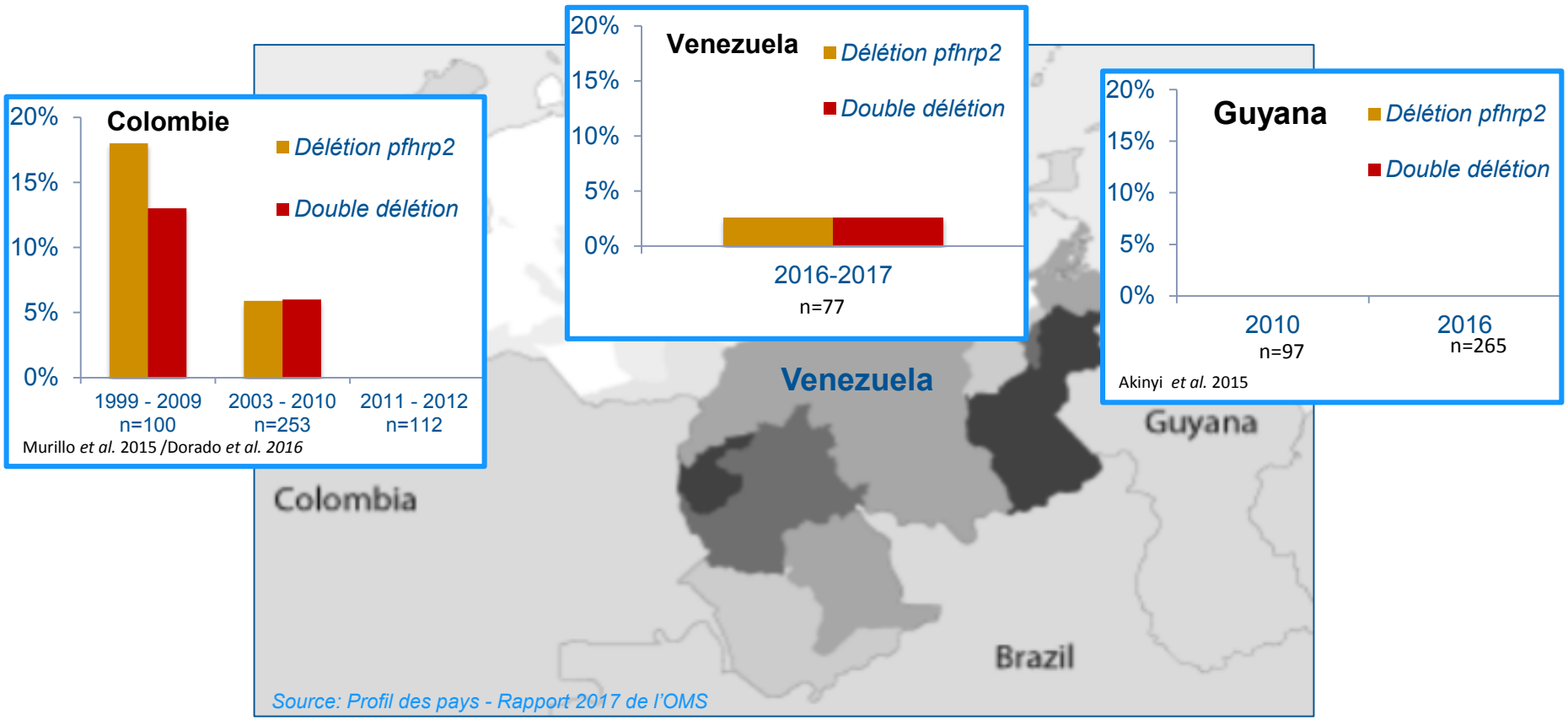
0.4 A low deletion prevalence in Venezuela



➢ **Need to be confirmed in a sample set of around 350 samples**

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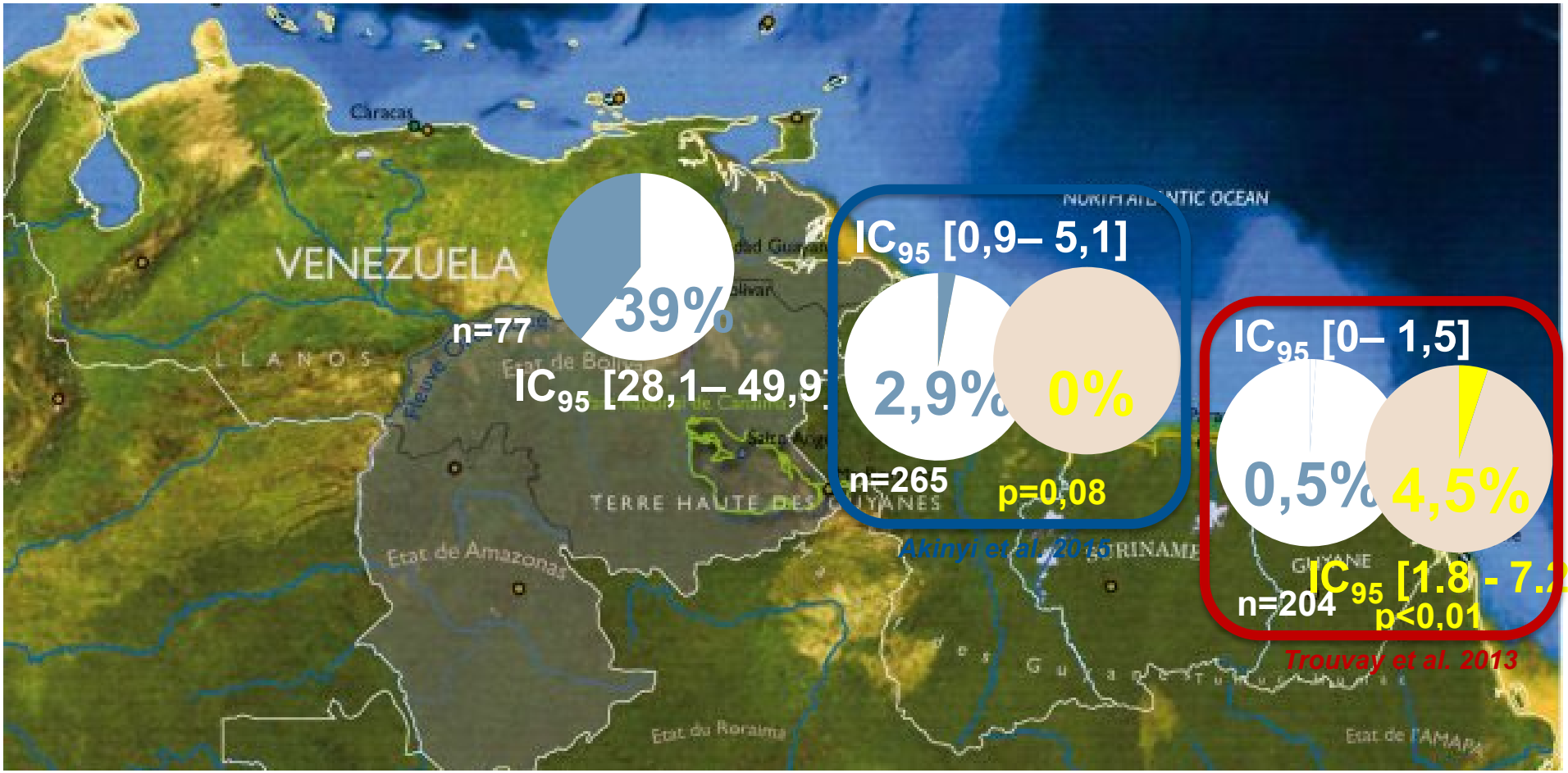
0.5 *pfhrp3* deletion in the Guiana Shield



➢ **Limited impact on RDT sensitivity alone**

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Thank you for your attention

Parasitology lab – NRC Malaria

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S. Roques
N. Guinguincoin

Guyana's partners

H. Cox
J. Seme

Regional and international partners

- **MoH**
- **Clinicians, medical biologists**
- **PAHO**
- **WHO-GMP**
- **CDC**