Etude multicentrique sur la disponibilité, l'accessibilité et la qualité des antiépileptiques en Afrique

***Programme QUAEDAf (QU**ality of **A**nti**E**pileptic **D**rugs in sub-Saharan **Af**rica)*

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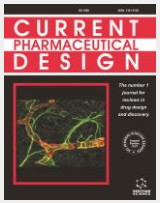
General background – specificity in developing countries

Current Pharmaceutical Design, 2017, *23*, 1-9 1

REVIEW ARTICLE

Antiepileptic Treatments in Developing Countries



Jeremy Jost[1,*], Athanase Millogo[1,2] and Pierre-Marie Preux[1]

[1]*INSERM, Univ. Limoges, CHU Limoges, UMR_S 1094, Tropical Neuroepidemiology, Institute of Neuroepidemiology and Tropical Neurology, CNRS FR 3503 GEIST, F-87000 Limoges, France;* [2]*Département de Médecine, CHU Souro Sanou, 01 BP 676, Bobo-Dioulasso, Burkina- Faso*

Treatment Gap: proportion of patients living with epilepsy who require treatment but not properly treated Kale, 2001

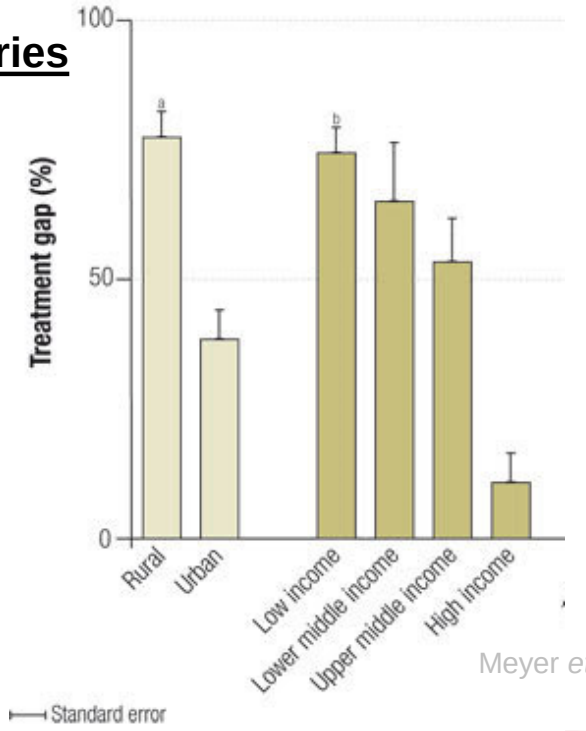
→ more than 75% in developing countries

Causes of a « diagnostic » treatment gap

- Mistakes
- No paraclinical examinations or trained staff
- No access to health system (distance and/or cost)
- Misbeliefs

Causes of treatment gap

- Low availability
- Low affordability
- Low quality



Meyer *et al*, 2009

Could AEDs quality be a problem for the patients

Meta-analysis of substandard and falsified medicines (all type)

- 96 studies
- 13.6% (95% CI, 11.0%-16.3%) *Ozawa et al., 2018*

- Regional prevalence
  - ➢ 18.7% in Africa
  - ➢ 16.3% in SSA for cardiovascular drugs *Antignac et al., 2017*

➢ For AEDs, Poor quality? only few assessments

Laroche et al., 2005	*13.7%*	*PB*	*4 parameters*
Mac et al., 2008	*65.0%*	*PB, VPA, CBZ, PHY*	*2 parameters*
Nizard et al., 2016	*3.0%*	*PB, CBZ, DZ*	*2 parameters*

- ✓ mass uniformity
- ✓ AI assay
- ✓ resistance
- ✓ disintegration
- ✗ dissolution

- ✓ mass uniformity
- ✓ AI assay
- ✗ resistance
- ✗ disintegration
- ✗ dissolution

➢ Falsified medicines for AEDs ?

Otte et al., 2015 ***Guinea-Bissau and Nigeria***

*« **PB** concentrations in tablets […] extremely low (0.8–1.5%) »*

Counterfeit antiepileptic drugs threaten community services in Guinea-Bissau and Nigeria

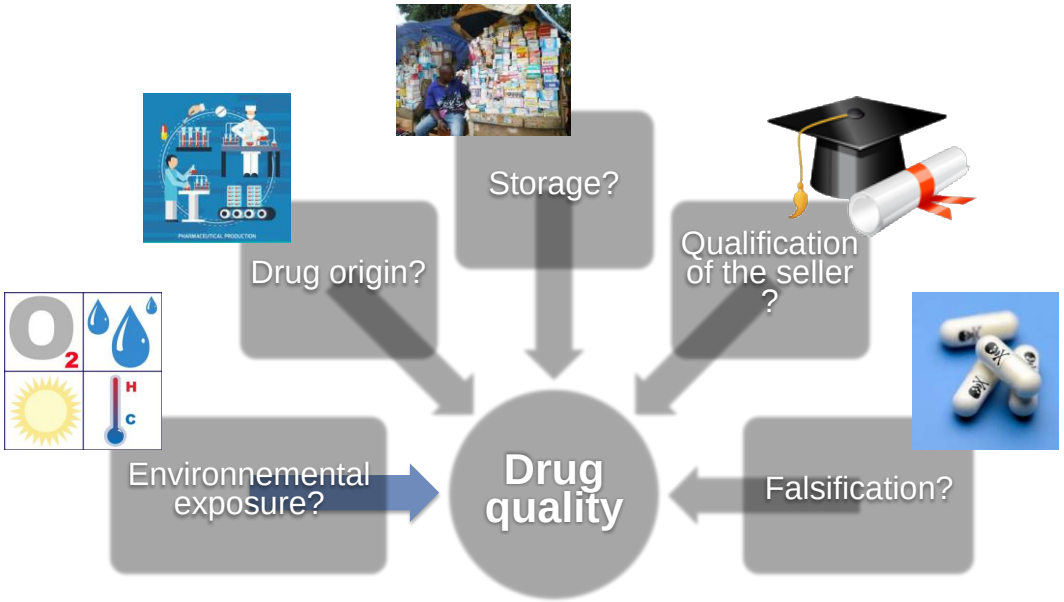
*Ozawa et al. **JAMA Netw Open. 2018;1(4):e181662***
*Antignac et al. **JAMA Cardiol. 2017 Feb 1;2(2):223-225***
*Laroche et al. **Epilepsia. 2005 Aug;46(8):1293-6***
*Mac et al. **Epilepsy Res. 2008 Jul;80(1):77-82***
*Nizard et al. **Seizure. 2016 Oct;41:134-40***
*Otte et al. **Lancet Neurol. 2015 Nov;14(11):1075-6***

Objectives of the QUAEDAf program

*(**Q**uality of **A**nti**e**pileptic **d**rugs in sub-Saharan **Af**rica)*

1. **Main objective**
   - To measure the **degree of quality** of AED samples from patients point of view

2. **Secondary objectives**
   - To evaluate the **proportion of falsified** drugs
   - To measure AEDs **availability**, **affordability** and **costs**
   - To assess **association** between quality and exposure variables



- Study design and Method

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Methods

Study design: multicentre cross-sectional study (9 countries)

Sampling: *every delivery structure where a patient could obtain AEDs*

- Official circuits (public/private) and illicit market if possible
- Urban and rural areas

Analyses: in France

→ *WHO prequalified laboratory*

→ *according to Pharmacopeia*

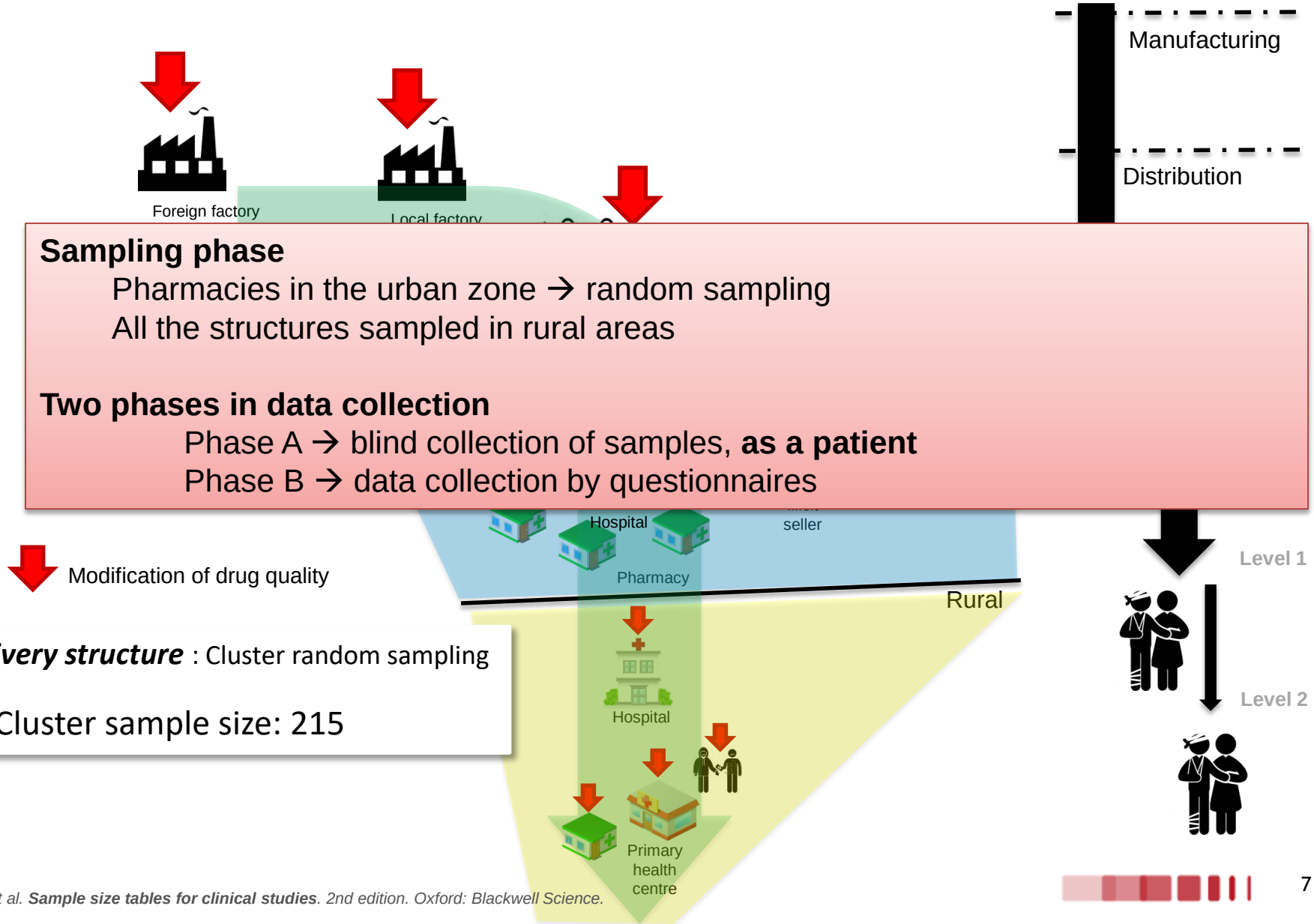
Inclusion criteria:

- Solid forms
- AEDs on the 19th WHO List of Essential Medicines

Ethical clearance obtained in each country

Fund: Sanofi Global Health Programs

Sampling



Sampling phase

Pharmacies in the urban zone → random sampling

All the structures sampled in rural areas

Two phases in data collection

Phase A → blind collection of samples, **as a patient**

Phase B → data collection by questionnaires

Delivery structure : Cluster random sampling

→ Cluster sample size: 215

Machin et al. ***Sample size tables for clinical studies****. 2nd edition. Oxford: Blackwell Science.*

Obj.: Quality of AEDs

Results

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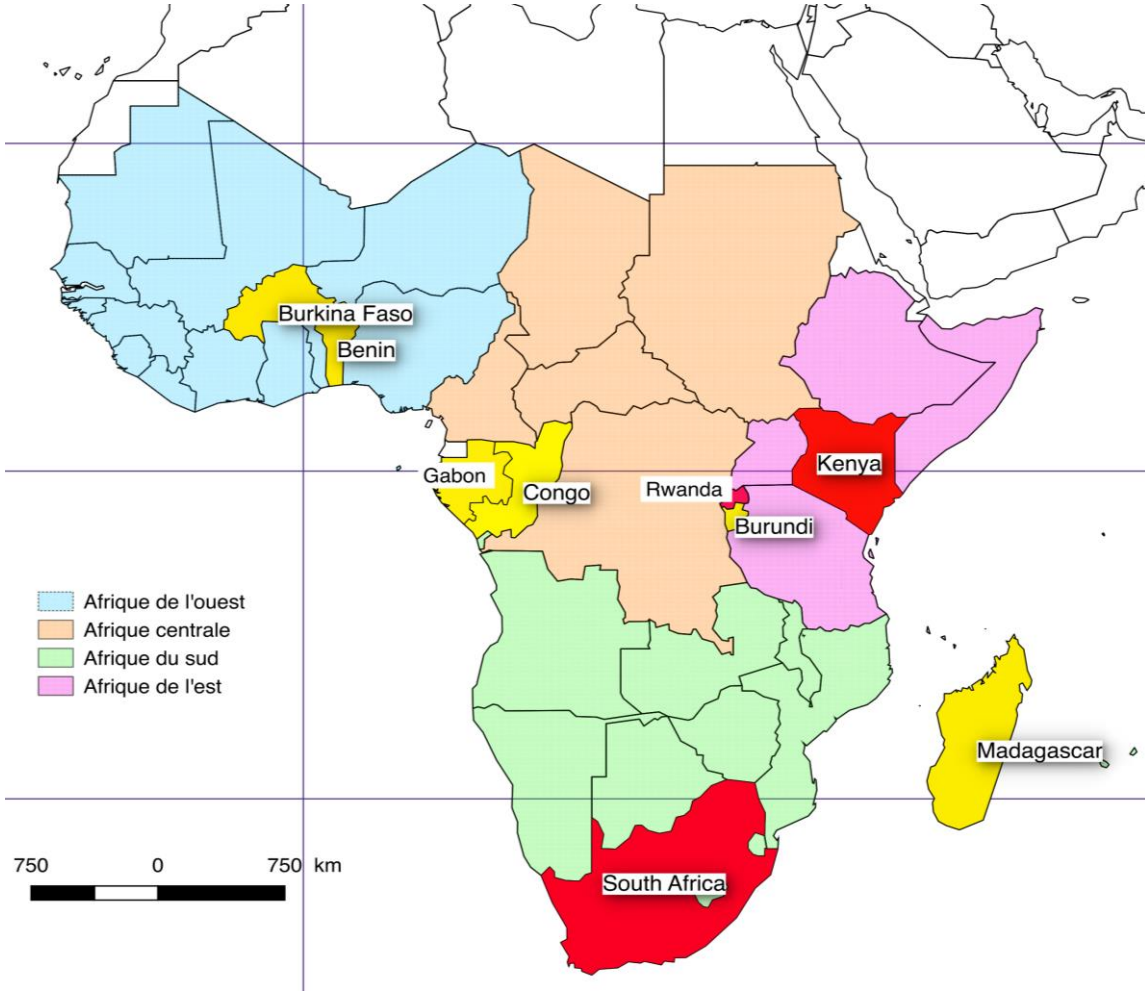
Results - sampling

	Number of clusters	Number of tablets
Gabon	6	1 440
Kenya	12	512
Madagascar	31	1 830
Burundi	41	3 401
Burkina-Faso	19	2 100
Rwanda	32	7 695
South Africa	13	1 622
Benin	29	1 230
Congo	41	1 620
TOTAL	224	21 450



Results - Quality

FULL-LENGTH ORIGINAL RESEARCH

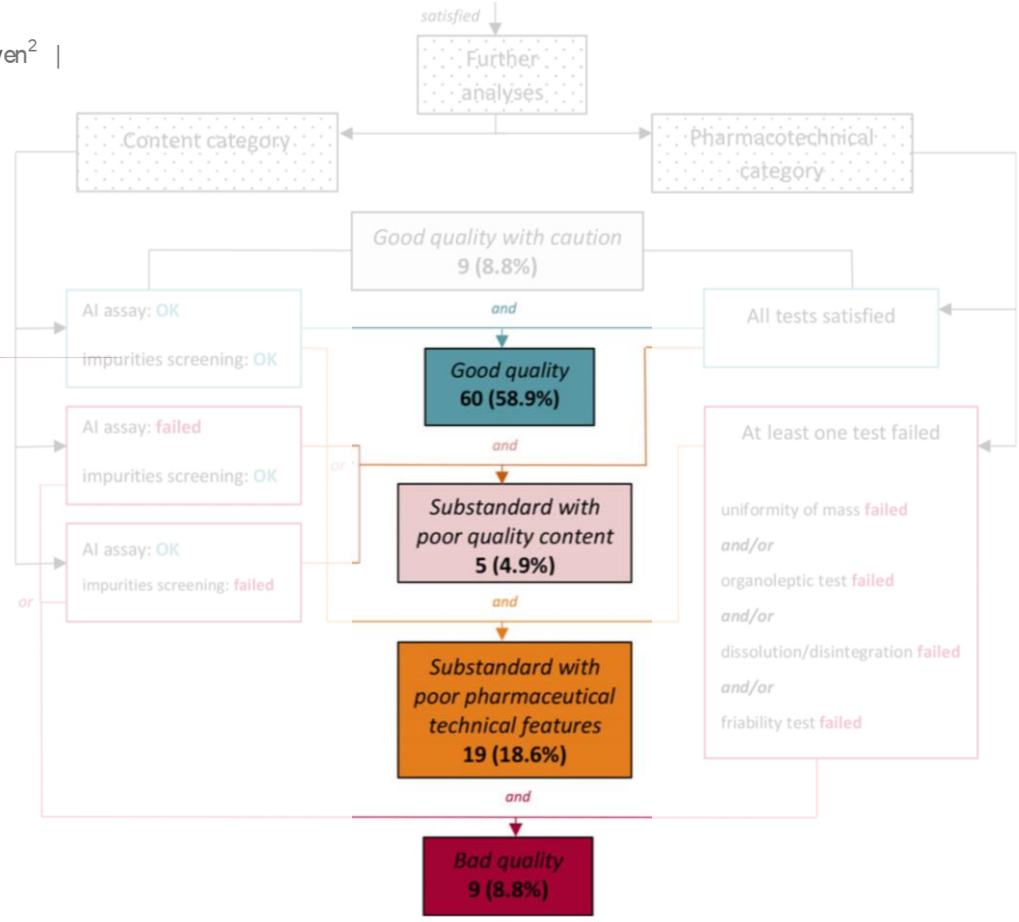
Epilepsia

Quality of antiepileptic drugs in sub-Saharan Africa: A study in Gabon, Kenya, and Madagascar

Jeremy Jost[1] | Voa Ratsimbazafy[1] | Thu Trang Nguyen[2] | Thuy Linh Nguyen[2] |

- **32.3%** of poor quality
- No country difference (p= 0.7)
- No falsified AED

	CBZ		VPA		PHY		PB
	%	N batches	%	N batches	%	N batches	%
Good quality	58.0	18	50.0	14	16.7	1	70.6
Substandard with poor quality content			17.9	5			
Substandard with poor pharmacotechnical features	38.7	12			83.3	5	5.9
Good quality with caution	3.3	1					23.5
Bad quality			32.1	9			
N total		31		28		6	



Results – Quality / Association

FULL-LENGTH ORIGINAL RESEARCH

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Multinomial logistic backward stepwise regression
X: degree of quality

		GQ (ref.)		SubAI		SubPTF		BQ		multivariate			
										SubPTF		BQ	
		%	n	%	n	%	n	%	n	RRR	p	RRR	p
Study area	Urban	67.9	55	6.2	5	**8.6***	**7**	17.3	14				
	Rural	66.7	14	0	0	**33.3***	**7**	0	0				
Supply chain feature	Public	55.6	10	0	0	**33.3***	**6**	11.1	2	9.9	0.04		
	Private	69.0	49	7.0	5	9.9	7	14.1	10				
	Illicit	76.9	10	0	0	7.7	1	15.4	2				
Without packaging	Primary	16.7	1	0	0	0	0	**83.3***	**5**				
	Secondary	59.5	22	0	0	13.5	5	**27.0***	**10**				
Manufactured in	EU	64.6	31	10.4	5	**2.1***	**1**	**22.9****	**11**				
	China	23.1	3	0	0	**77.0**	**10**	0	0	119.8	<0.0001		
	India	76.2	16	0	0	9.5	2	14.3	3				
	Africa	95.0	19	0	0	**5.0***	**1**	0	0				
	Brand	66.1	39	8.5	5	**3.4***	**2**	**22.0****	**13**				
	Generic	69.8	30	0	0	**27.9***	**12**	**2.3****	**1**				
Active ingredient	CBZ	61.3	19	0	0	**38.7***	**12**	0	0				
	VPA	50.0	14	17.9	5	0	0	**32.1***	**9**				
	PHY	16.7	1	0	0	0	0	**83.3***	**5**				
	PB	94.1	32	0	0	**5.9***	**2**	0	0				
	wind	62.2	23	2.7	1	10.8	4	**24.3***	**9**			5.4	0.03
Environmental exposure	Dust	60.0	27	2.2	1	**17.9***	**8**	**20.0****	**9**				
	moisture	60.5	23	2.6	1	13.2	5	**23.7***	**9**				
	Air-conditionning	68.4	39	7.0	4	0	0	24.6	14				

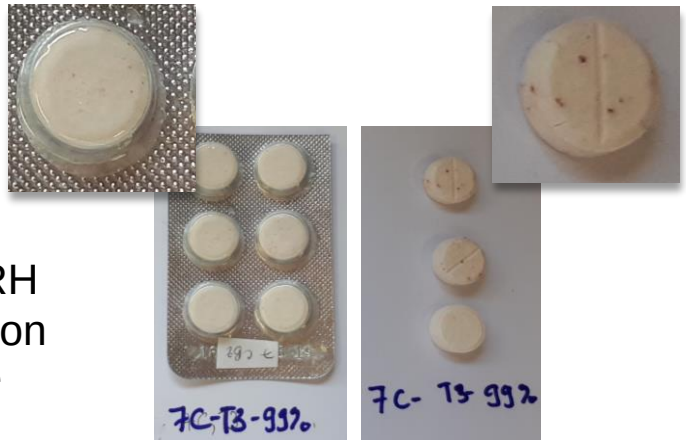
Public facilities

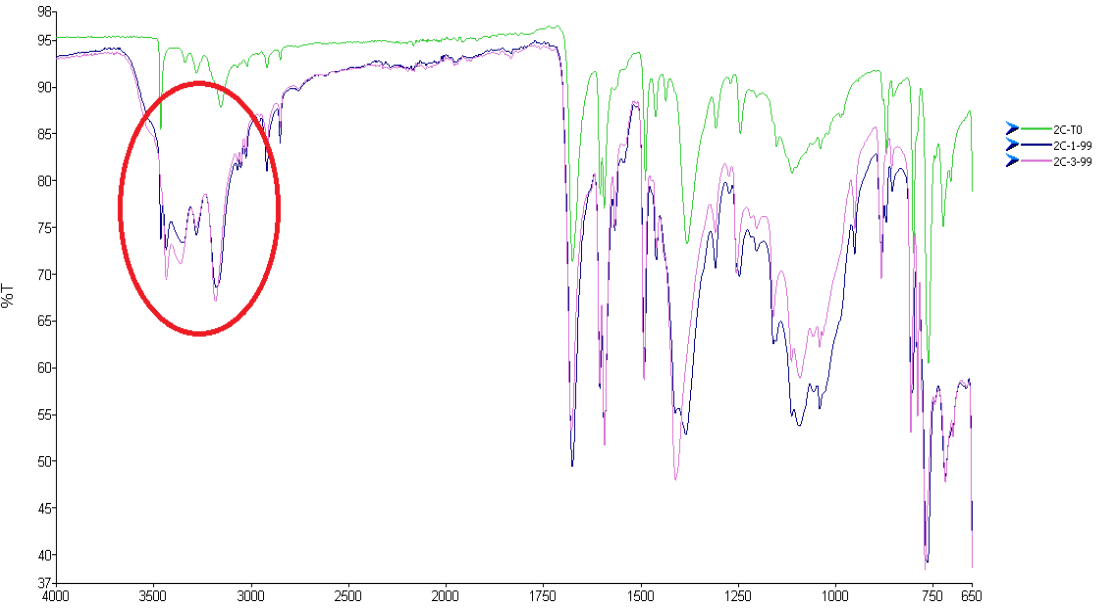
China manufacturing

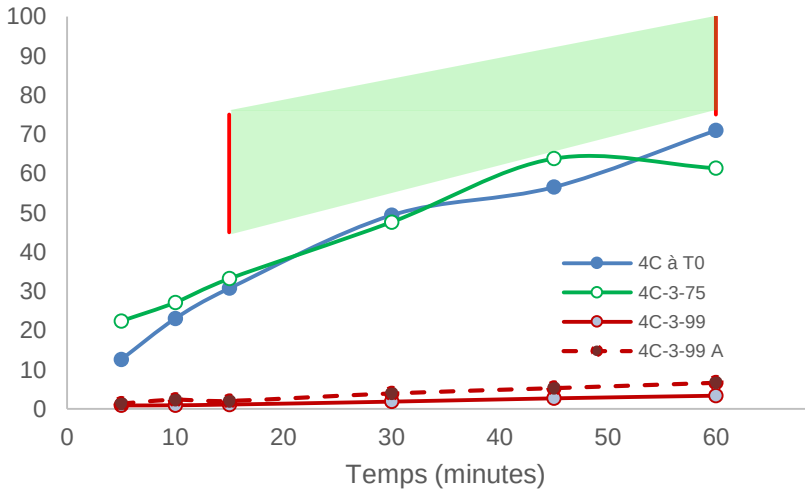
Uncontrolled atmosphere

STAETrop: Carbamazepine

- Sensibility for humidity
- As from 1 month 99% RH
- Polymorphic conformation
  - Form III → di-hydrate
  - DSC and ATR-FTIR

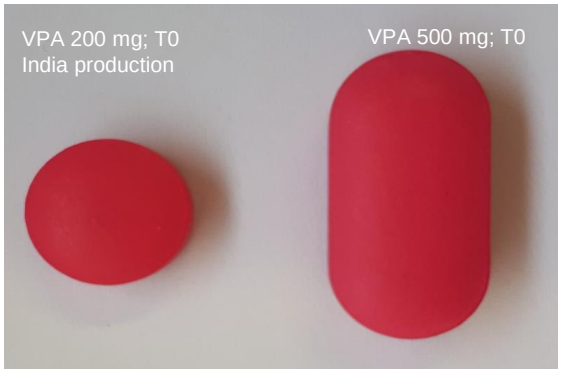






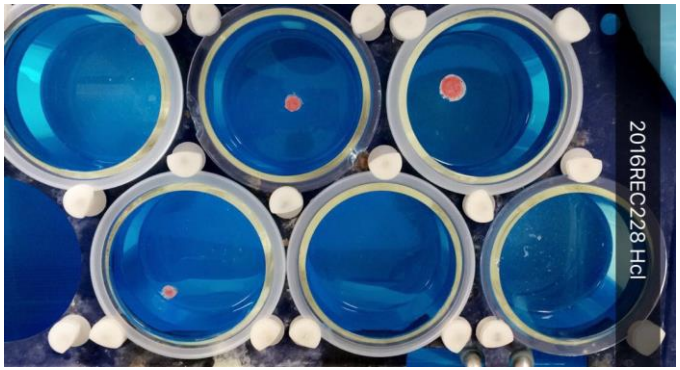
*Jost et al. **Epilepsia. 2018;00:1-11***

STAETrop: Sodium Valproate



- Highly sensible for humidity
- As from 1 day
  - 75% RH

- Without desiccant cap
- Loss of coating and so gastro-resistance feature



Obj.: Availability and affordability

- Brief background
- Study design and Method

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Brief background

Treatment gap's economic dimensions

Mbuba et al., 2008; Meinardi et al., 2001; Ratsimbazafy et al., 2011; Scott et al.,2001

- high cost of drugs
- unavailability of drugs, no price regulation

PB as a first-line treatment

- US$ 5 per year *Scott et al., 2001*
- Lao US$ 30 per year *Chivorakoun et al., 2012*

CBZ, PHY and VPA are respectively 5, 10 and 15 times **more expensive than PB** *Scott et al., 2001*

Cameron et al., 2012

- 46 countries
- availability of generic in the public sector: **< 50%**
- availability of generics in the private sector: **42% PHY to 69% PB**
- originator brands: **30 times more expensive**

*Mbuba et al. **Epilepsia. 2008 Sep;49(9):1491-503***
*Meinardi et al; **Epilepsia. 2001 Jan;42(1):136-49***
*Ratsimbazafy et al. **Trop Doct. 2011 Jan;41(1):38-9***
*Scott et al. **Bull World Health Organ. 2001;79(4):344-51***
*Chivorakoun et al. **Rev Neurol (Paris).2012 Mar;168(3):221-9***

Method - Data collection

- **Availability:** % of outlets dispensing AEDs
  - ***Private sector***
    → All registered structures *(up-to-date list of authorized structures)*
  - ***Public** and illicit sector*
    → Data collection at specific visits

Interview:
10 minutes

- **Affordability:** number of days' wages that the lowest-paid government worker would need to purchase a month's supply of AEDs

Monthly treatment costs → Defined daily dose (WHO database)

	DDD
Phenobarbital	0.1 g
Carbamazepine	0.8 g
Sodium valproate	1.5 g
Phenytoine	0.3 g

Price standardization and adjustement

Obj.: Availability and affordability

- Results

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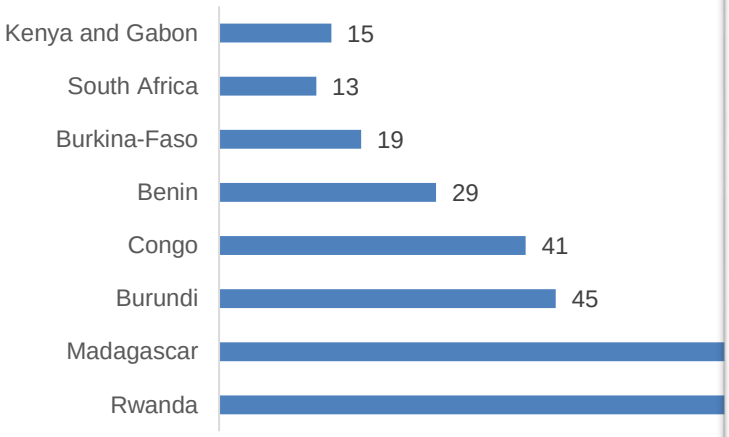
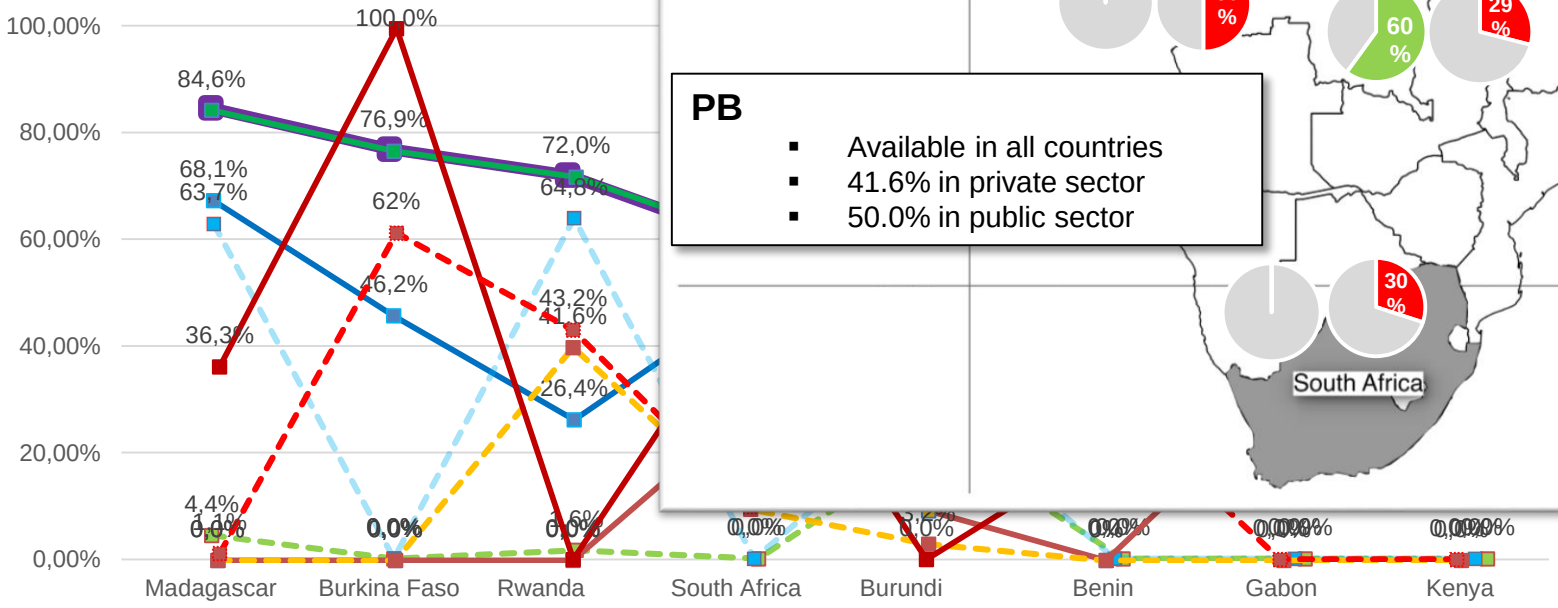
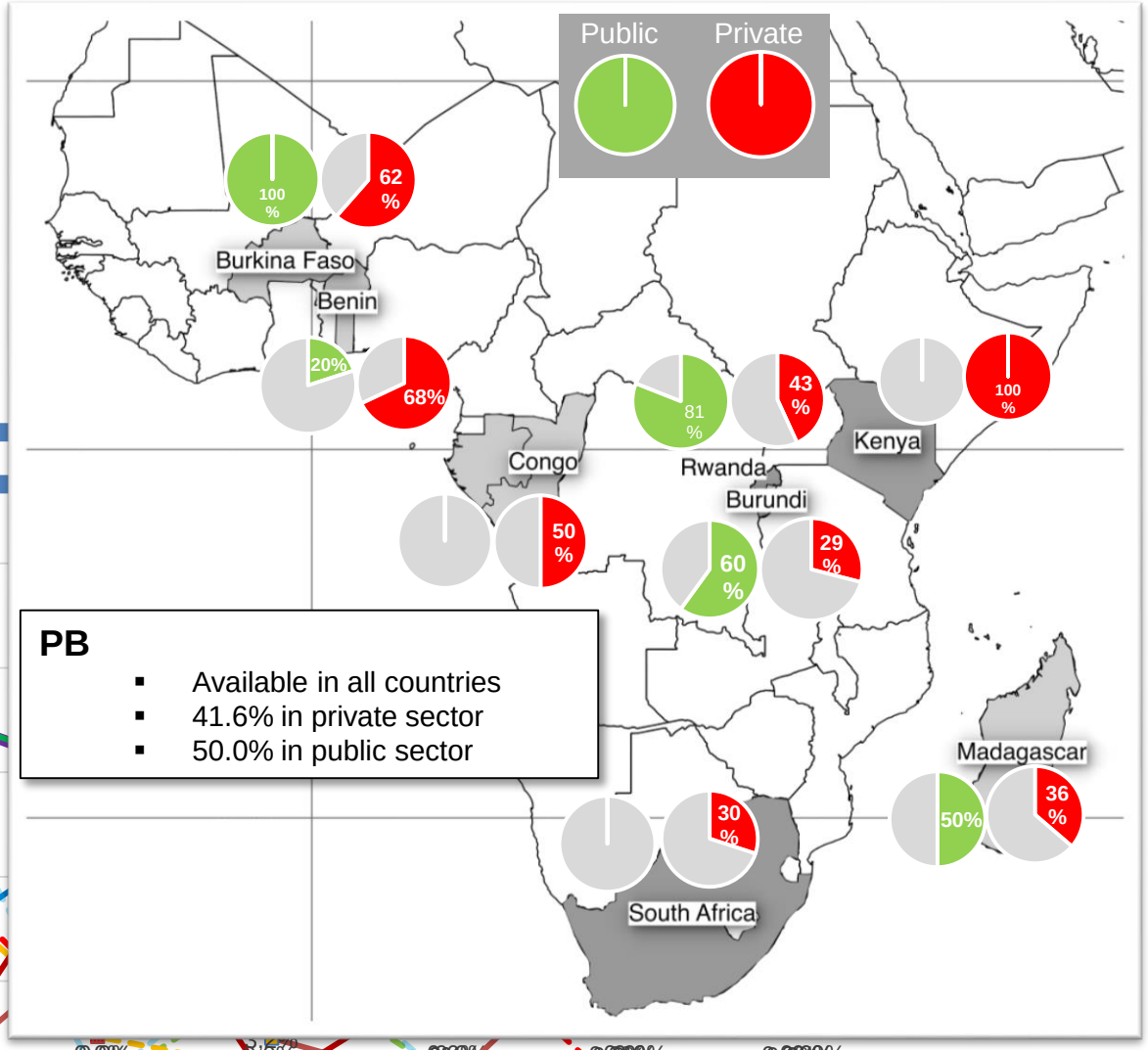
Availability

- **386 structures investigated**





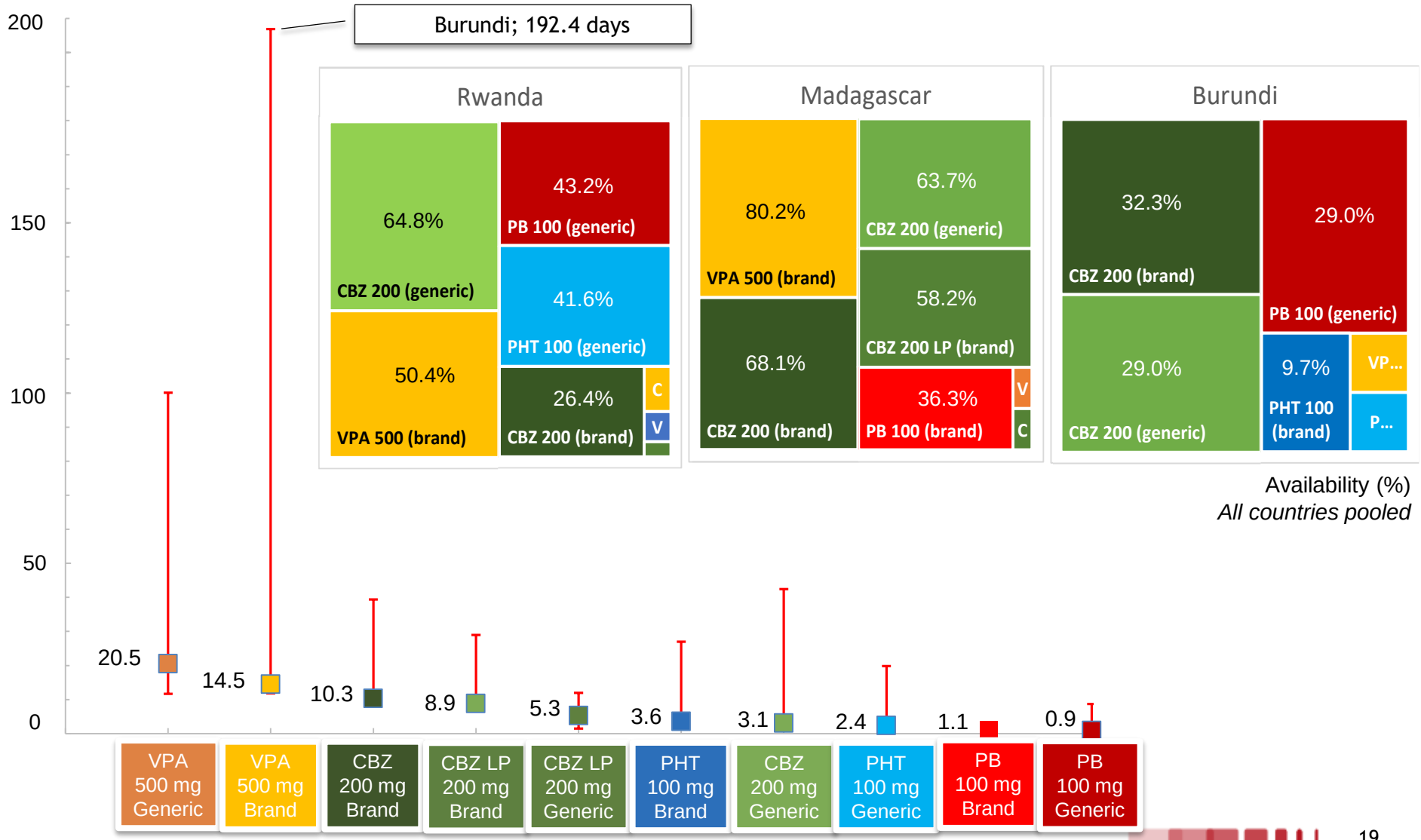


PB

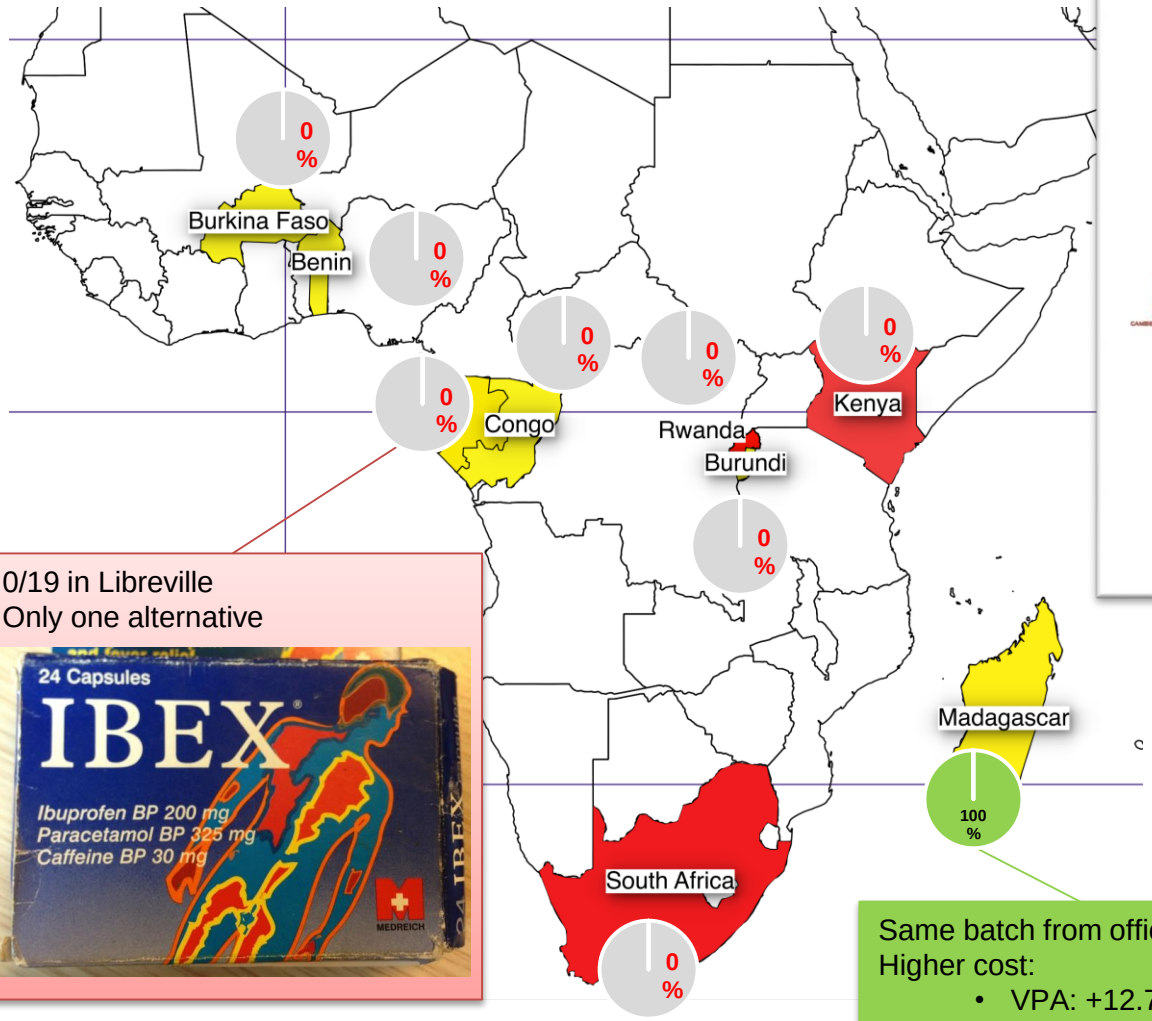
- Available in all countries
- 41.6% in private sector
- 50.0% in public sector

Affordability

Expressed in day's wages to purchase a month's supply *(all countries pooled)*



Informal market



0/19 in Libreville
Only one alternative

Same batch from official circuit
Higher cost:

- VPA: +12.7%
- CBZ: +54.3%
- PHY: +62.5%

*Jost et al., **SpringerPlus 2016 Oct 6;5(1):1726. eCollection 2016.***

Discussion and conclusion

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Key messages

1 **32.3%** were of poor quality

2 **VPA** and **CBZ** were the most sensitive to tropical conditions (humidity)

3 **Local manufacture** of PB → highest quality

4 **Uncoated forms** → the most sensitive to environmental factors

5 **Storage conditions** were almost systematically unfavorable

6 **Public supply chain** → worst availability

7 **Private supply chain** → main **supply chain for AEDs**

→ least affordable

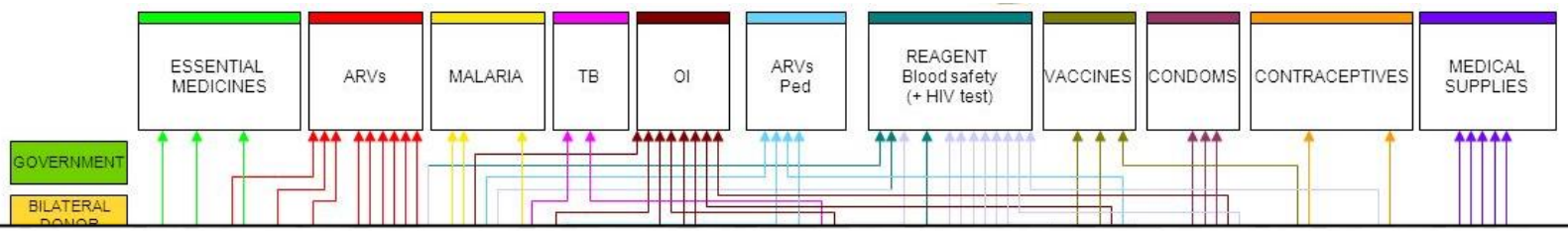
8 **Generics** → most affordable, least available

→ High heterogeneity of promotion

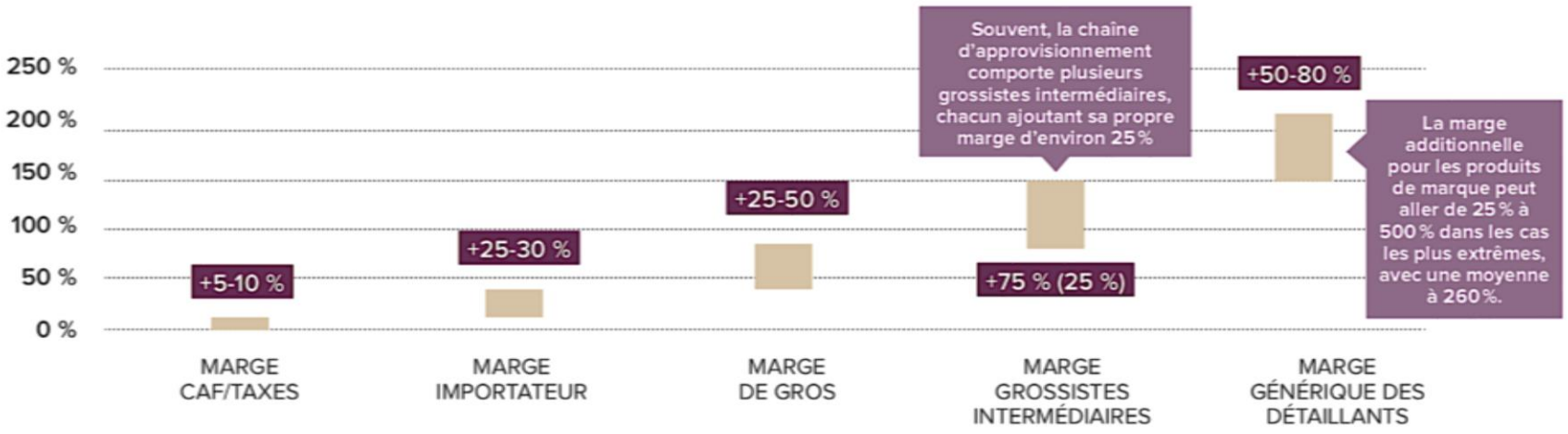
9 **PB** → most affordable but the least available in the private sector

- **VPA** Prolonged Release Tablets : **unaffordable**

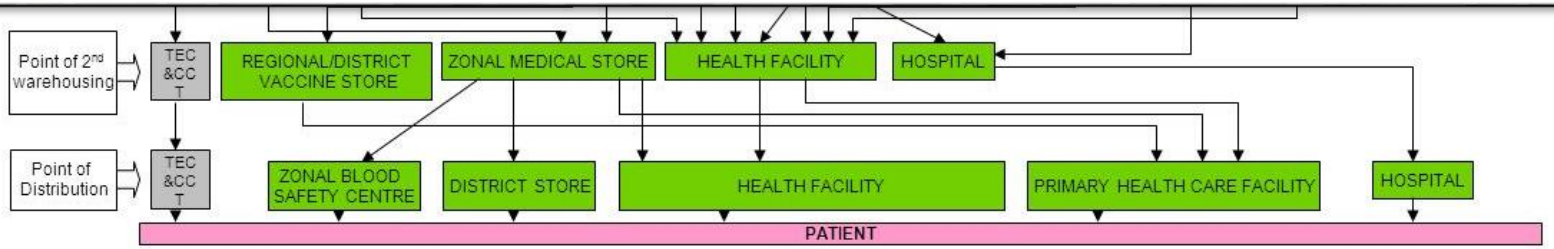
Discussion – a too segmented market



Majorations moyennes des prix des médicaments sur les marchés émergents



Source : International Finance Corporation (IFC), *Private Sector Pharmaceutical Distribution and Retailing in Emerging Markets*, 2017



Senegal Ministry of Health/Central Medical Store; cited in WHO 2013 report

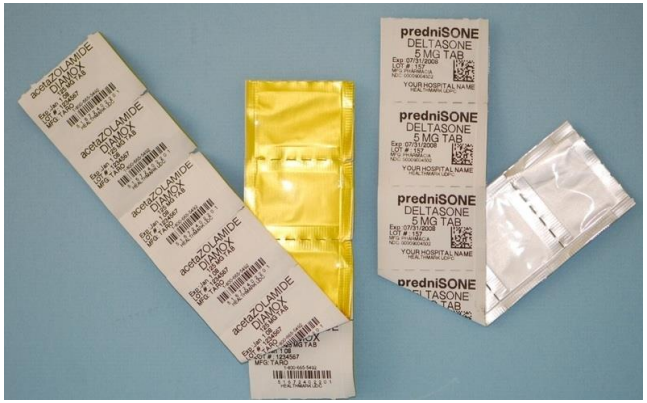
Discussion

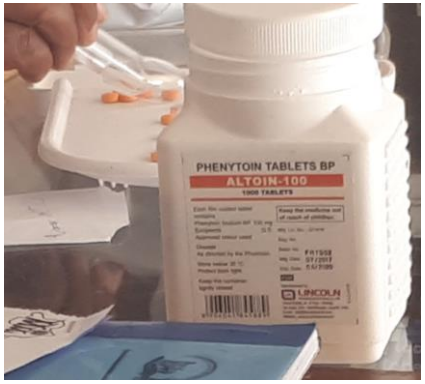
- Primary and secondary packaging are major

- Storage conditions

- Unpacking → common practice
  - Managed
  - Secured

- Conditioning process





Recommendations

- **Strengthen pharmacists** + drug-providing health professionals **role**
  →to improve **adherence**,
- Raise awareness
  - **storage conditions**,
  - about the role of **primary** and **secondary packaging**
- **Secure re-packaging**
- Develop **galenic** forms with a protective coating
- Encourage **local production**
- Encourage the use of **generic forms**
- Include AEDs in the **WHO pre-qualification program**

World Health Organization


Thank you for your attention
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