

# First results of the Titi study

Benin, Burkina Faso, Cameroon and Central African Republic

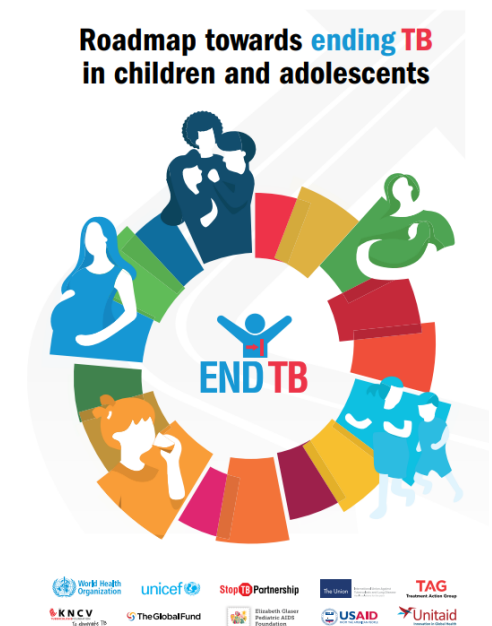
Valérie Schwoebel

Childhood TB Working Group meeting

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# Background

- Over 50% of the estimated number of tuberculosis cases in children 0-14 years (~ 1 Million) are not reported (~70% of under 5)
- 80% of the TB deaths in children occur in children under 5
- While contact investigation and preventive therapy is strongly recommended for children under 5, over 75% of eligible children still do not access preventive therapy
- Following a workshop organized by The Union in 2014 with national TB programs (NTP) and paediatricians from 10 countries in francophone Africa, implementation of contact investigation and preventive therapy was selected as a priority action
- A study was launched in 2015 in 4 countries with financial support of the French 5% Initiative



# Objectives

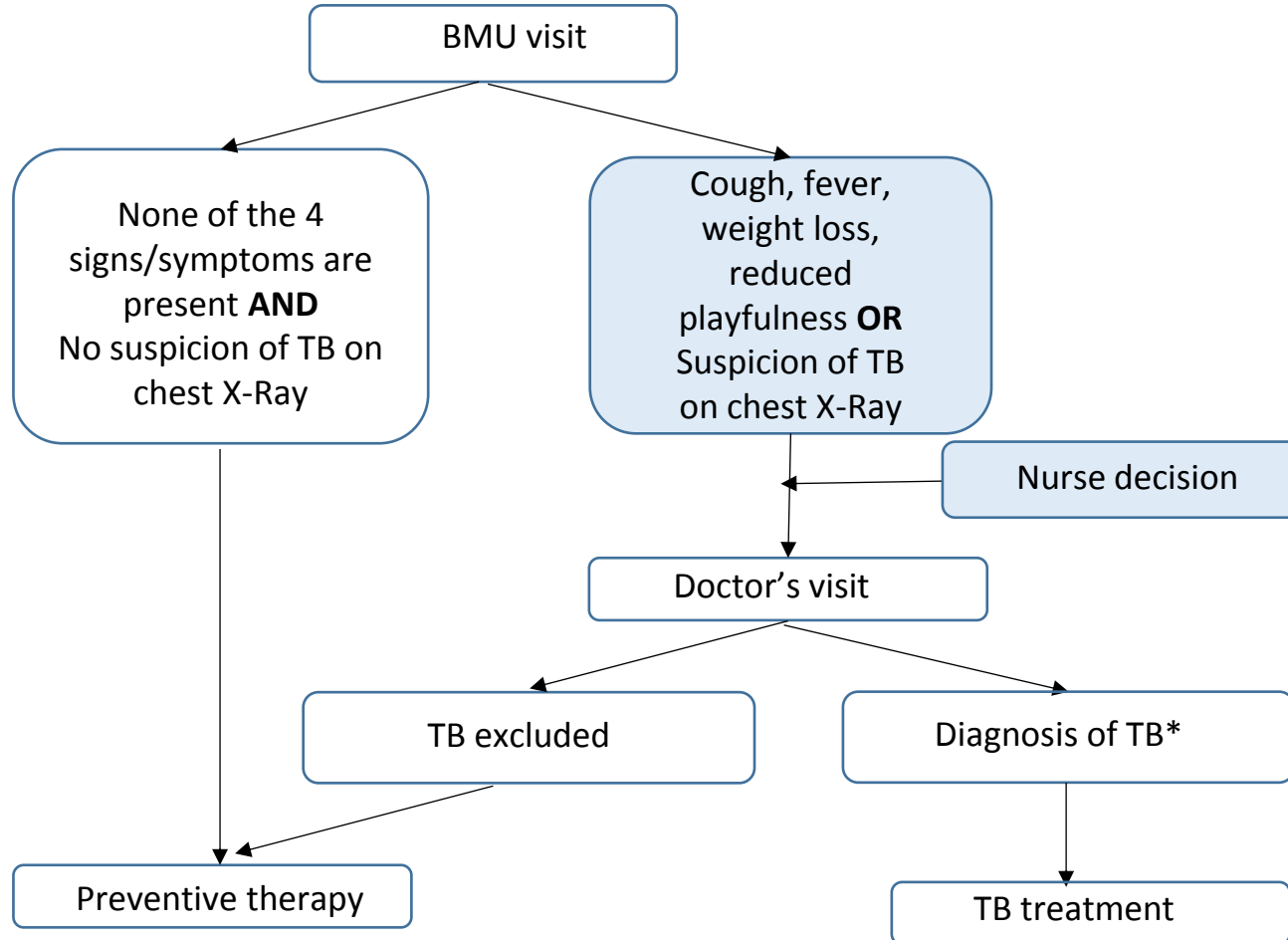
The aim was to demonstrate the feasibility and document the effectiveness of contact investigation and preventive therapy for children < 5 years of age within the framework of NTP, with five specific objectives

- **Estimate the number of children < 5 contacts of bacteriologically confirmed PTB cases (PTB+)**
- **Determine the prevalence and risk factors for active TB and for TB infection at inclusion**
- Determine the incidence of active TB during and after preventive therapy
- **Assess children adherence to preventive therapy and adverse drug events**
- Develop simple standardised recording & reporting tools

# Methods (1) - Inclusion

- Study period : April 2016 to September 2017 (18 months)
- Study sites
  - Benin, Burkina-Faso, Cameroon and Central African Republic
  - 13 basic management units in 4 large cities: Cotonou (1), Ouagadougou (4), Douala (4) and Bangui (4)
- Study population: all adults with recently diagnosed PTB+ were eligible if
  - Residence within ~ 5 km of the BMU
  - Permanent residence for > 3 months
  - Children < 5 years living at home
- Patients were enrolled after informed consent for a home visit by nurse+social worker
  - Family questionnaire : house, family structure, type of contacts
  - Child questionnaire: symptoms, first physical examination,
  - Tuberculin skin test (TST), appointment for BMU visit and chest X-Ray

# Methods (2) – Screening procedure



Blind review of random sample of chest X-Rays:

- 100% “suspicion TB”
- 25% “normal” or “other” by independent team (radiologist / pediatric pneumologist) in Lausanne

\* Gastric aspirate

- Smear
- Xpert MTB/RIF
- Culture if available

# Methods (3) – Preventive therapy

- Regimen

- 6 months of isoniazid (6H) in Benin

<i>Weight bands</i>	<i>Isoniazid (mgs)</i>	<i>H50 tablet</i>	<i>H100 tablet</i>
4-7kg	50	1	1/2
8-11kg	100	2	1
12-15kg	150	3	1 1/2
16-24 kg	200	4	2



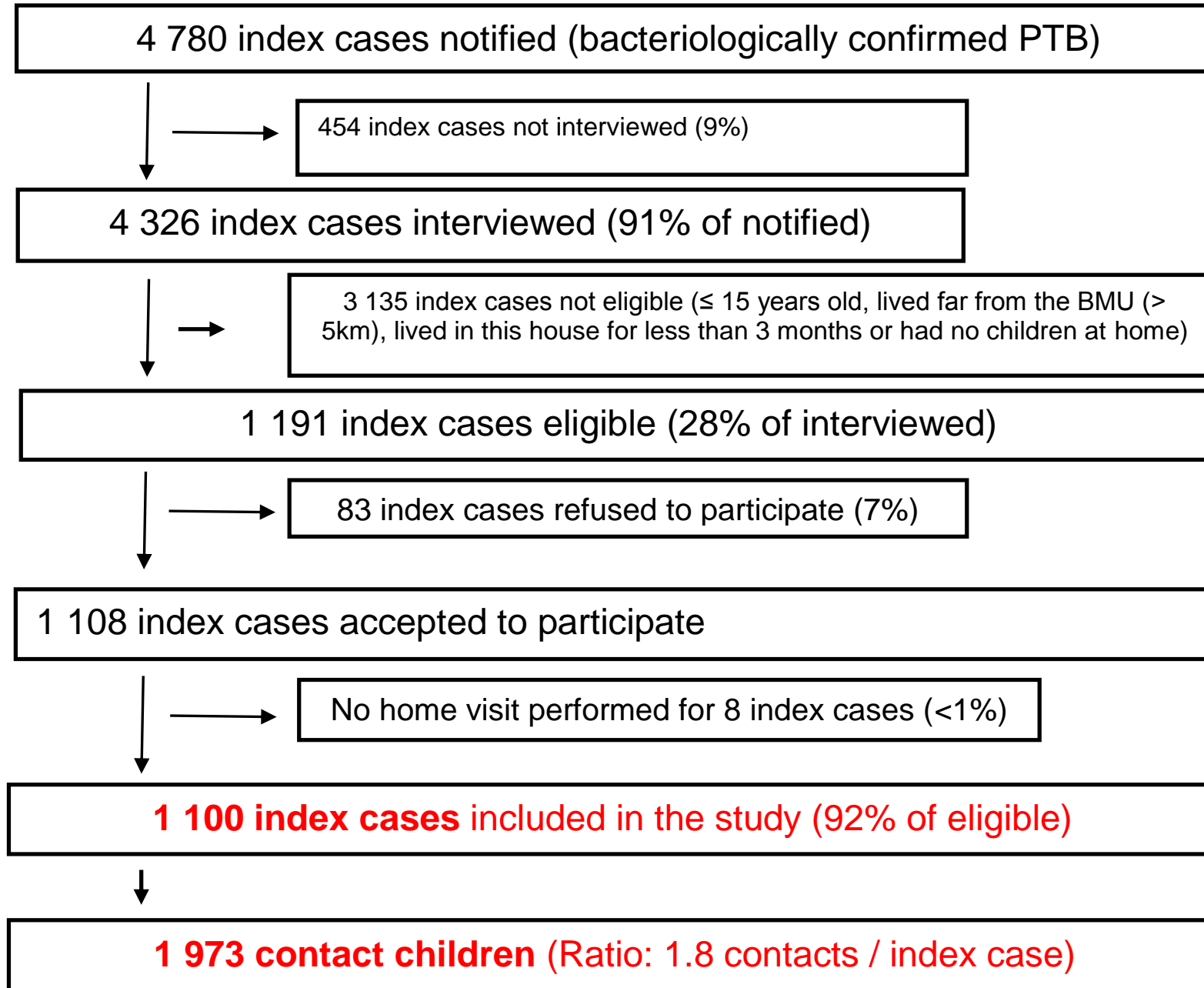
- 3 months of rifampicin+isoniazid (3 RH75/50) in Burkina, Cameroon and CAR

<i>Weight bands</i>	<i>RH 75/50 tabs</i>
4-7kg	1
8-11kg	2
12-15kg	3
16-24 kg	4

- Monthly visits during treatment : adherence, symptoms, side effects
- 3-monthly visits up to 12 months after treatment termination

# Results

# Inclusion



no significant difference in patients characteristics between index cases who accepted to participate and those who did not



# Number of children at home

Country	% PTB+ with children < 5 at home	Nb index cases included (I)	Nb. contact children included (C)	C/I Ratio in study	C/I Ratio in PTB+
Bénin	<b>44.7</b>	223	490	2.2	1.0
Burkina-Faso	<b>51.3</b>	285	454	1.6	0.8
Cameroun	<b>42.1</b>	323	505	1.6	0.7
RCA	<b>46.3</b>	269	524	1.9	0.9
<b>Total</b>	<b>45.8</b>	<b>1100</b>	<b>1973</b>	<b>1.8</b>	<b>0.8</b>

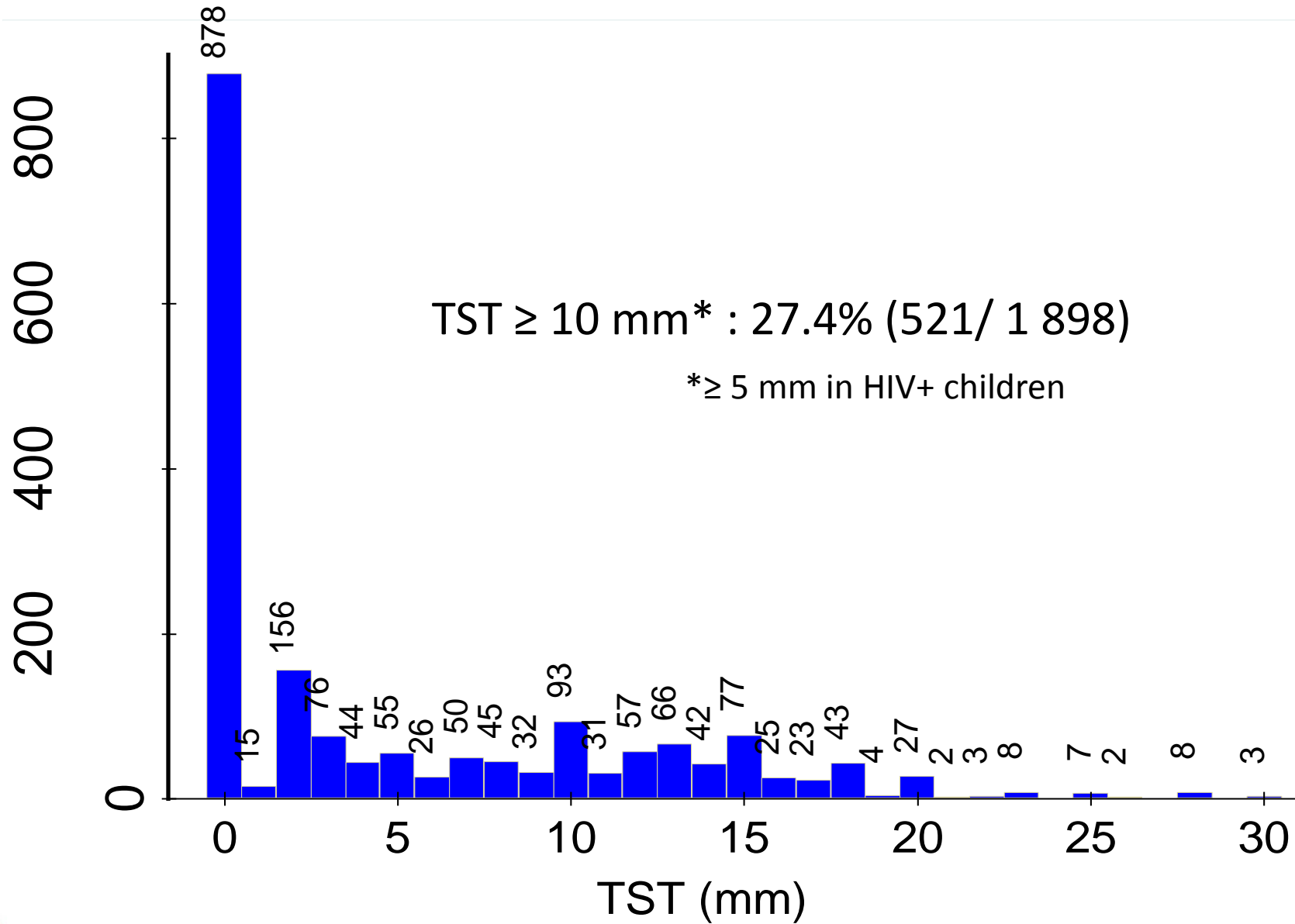
# Children characteristics (N=1973)

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	%
<b>Sexe (Male)</b>	50
<b>Mean age [CI95%]</b>	31 months [30.2 - 32.2]
<b>Malnutrition (z-score &lt; 2 SD)</b>	18
<b>BCG vaccination</b>	93
<hr/>	
<b>Sleep at home within the last 3 months</b>	80
<b>Contact with index case (everyday)</b>	66
<b>Play with index case (everyday)</b>	61
<b>Eat with index case (everyday)</b>	40
<b>Sleep in the same room with index cases (everyday)</b>	46
<b>Sleep in the same bed with index cases (everyday)</b>	39

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# Tuberculin skin test results



# Risk factors for $\geq 10$ mm TST result

	Univariate analysis OR [95%CI]	Multivariate analysis aOR* [95%CI]
<b>Sexe (male)</b>	1,24 [1,01 - 1,52]	1,27 [1,03 - 1,57]
<b>Age category (<math>\leq 24</math> months)</b>	1.02 [0.83 - 1.26]	-
<b>Sleep at home the last 3 months</b>	1,01 [0,85 - 1,42]	-
<b>Contact with index case (everyday)</b>	1,69 [1,35 - 2,12]	NS
<b>Play with index case (everyday)</b>	1,32 [1,07 - 1,64]	1,53 [1,18 - 1,97]
<b>Eat with index case (everyday)</b>	1,06 [0,87 - 1,31]	-
<b>Sleep in the same room with index case (everyday)</b>	1,41 [1,15 - 1,73]	NS
<b>Sleep in the same bed with index case (everyday)</b>	1,58 [1,29 - 1,94]	1,84 [1,44 - 2,35]
<b>BCG vaccine</b>	1,51 [0,97 - 2,,33]	NS

\* Adjusted for country

# Initial screening

Signs/symptoms at home visit	%
Cough (any duration)	43
Fever	30
Reduced playfulness	16
Weight loss or reduced appetite	19
<b>Any of the 4 symptoms</b>	<b>61</b>
Any sign/symptom	75
Any respiratory sign/symptom	54
Temperature $\geq 38^{\circ}\text{C}$	4
TST $\geq 10$ mm ( $\geq 5$ mm in HIV-infected children)	27
Suspicion of TB on chest X-Ray	<b>14</b>
Referred to clinician	<b>29</b>

# Chest X-Ray

## 93% of children had chest X-ray performed

- Lesions recorded on standard form
- Local interpretation
  - 1st level : radiologist or pneumologist
  - 2nd level : study clinician (paediatrician or pneumologist)

## External review

- 3 countries (Benin, Burkina Faso, CAR) participated in the review
- 393 X-Rays evaluated blindly by 2 reviewers in Lausanne (gold standard)
- 60% X-rays complied with quality standards
- Inter-reader agreement with reviewers was graded as «slight »
  - **Kappa=0.14** [0.09 – 0.17] with 1st level local reader
  - **Kappa=0.10** [0.06 – 0.20] with 2nd level local reader (study clinician)

Large inter-country differences

"TB" lesions on chest X-ray	%
Benin	18.2
Burkina Faso	1.3
Cameroon	5.9
CAR	26.9
<b>Total</b>	<b>14.4</b>

# Tuberculosis

## 105 « decision to treat » TB

Classification*	n	%
Possible pulmonary TB	8	7.6
Probable pulmonary TB	94	89.5
Confirmed pulmonary TB	2	1.9
Extrapulmonary TB	1	1.0
<b>Total</b>	<b>105</b>	<b>100.0</b>

- Diagnosis based on initial evaluation, although 17 cases were diagnosed after the child had started preventive therapy
- 102 received TB treatment : 88% success, 12% non evaluated

## No incident case during preventive treatment

Tuberculosis	N	n	%	p
Total	1973	105	<b>5.3</b>	
Country				p<0.001
Benin	490	25	<b>4.5</b>	
Burkina Faso	454	10	<b>2.2</b>	
Cameroon	505	8	<b>1.6</b>	
République Centrafricaine	524	62	<b>11.8</b>	
Age				
<=24 months	787	51	<b>6.5</b>	p=0.05
>24 months	1180	53	<b>4.5</b>	
No significant difference by gender, BCG vaccination				

\* Graham SM et al. Evaluation of Tuberculosis Diagnostics in Children: 1. Proposed Clinical Case Definitions for Classification of Intrathoracic Tuberculosis Disease. Consensus From an Expert Panel. JID 2012

# Preventive therapy

	Total		Benin		Burkina Faso		Cameroon		CAR	
	N	%	N	%	N	%	N	%	N	%
<b>Started preventive therapy</b>	1770	<b>89.7</b>	429	<b>87.6</b>	436	<b>96.0</b>	446	<b>88.3</b>	459	<b>87.6</b>
<b>Evaluation of observance</b>	1612	<b>91.1</b>	424	<b>98.8</b>	411	<b>94.3</b>	358	<b>80.3</b>	419	<b>91.3</b>
% of tablets taken		<b>98.1</b>		<b>98.2</b>		<b>98.0</b>		<b>99.0</b>		<b>97.2</b>
<b>Symptoms during preventive therapy</b>										
Yellow eyes	3	<b>0.2</b>	1	<b>0.2</b>	0	<b>0.0</b>	1	<b>0.2</b>	1	<b>0.2</b>
Vomiting	31	<b>1.8</b>	3	<b>0.7</b>	8	<b>1.8</b>	20	<b>4.5</b>	0	<b>0.0</b>
<b>Treatment outcome</b>										
Treatment completed	1632	<b>92.2</b>	424	<b>98.8</b>	403	<b>92.4</b>	404	<b>90.6</b>	401	<b>87.4</b>
Died	5	<b>0.3</b>	1	<b>0.2</b>	0	<b>0.0</b>	3	<b>0.7</b>	1	<b>0.2</b>
TT : Late start of TB treatment	17	<b>1.0</b>	2	<b>0.5</b>	7	<b>1.6</b>	0	<b>0.0</b>	8	<b>1.7</b>
TT : Adverse drug event	1	<b>0.1</b>	0	<b>0.0</b>	1	<b>0.2</b>	0	<b>0.0</b>	0	<b>0.0</b>
TT : RIF+ index case	1	<b>0.1</b>	0	<b>0.0</b>	1	<b>0.2</b>	0	<b>0.0</b>	0	<b>0.0</b>
Lost to follow-up	114	<b>6.4</b>	2	<b>0.5</b>	24	<b>5.5</b>	39	<b>8.7</b>	49	<b>10.7</b>



# Standardized tools

- Stamp with number of children for patient's card



- Chest X-Ray form

- Based on « template chest X-Ray review tool » (*Graham S. JID 2012*)
- 9 lesions (airway compression, lymphadenopathy, ....)
- Conclusion : 1/ normal 2/ abnormal suggestive of TB or 3/abnormal suggestive of other disorder

- Preventive therapy register

Month 0 Date		Month 1 Date		Month 2 Date		Month 3 Date		Result
Poids	Dose	Poids	Dose	Poids	Dose	Poids	Dose	
								TT (Treatment completed) PDV (lost to follow-up) DCD (death) F (transferred out) TB (tuberculosis) A (Treatment stopped by doctor, e.g. for adverse reaction)

# Discussion (1)

- Uncertainty around the ~ 5% estimated prevalence of TB
  - Low bacteriological confirmation
  - Wide inter-country differences
- Despite common protocol / training / tools, there were differences in the implementation of diagnostic procedures by NTPs due to differences in
  - Assessment of symptoms by nurses
  - NTP guidelines (e.g) : in Benin symptomatic children have to be referred to a MD
  - Medical practice and experience : experience in TB rare among pediatricians, experience in infants rare among pneumologists/radiologists
  - Interpretation of chest X-rays, particularly in infants
  - Referral procedures, bacteriological examinations

# Discussion (2)

- Interpretation of systematic chest X-ray was a real challenge
  - Consistent with findings of other authors (*Triasih 2015, Berteloot 2018*)
- Uptake of preventive therapy was good >90%
  - 92% completed treatment
  - Reported adherence was excellent in those who completed treatment, without difference according to the regimen used (6H vs 3RH)
- Very few adverse drug events reported, only one leading to treatment termination (3RH)

# Conclusion

- Contact investigation is feasible in the NTP context
- Ratio contact children / notified bacteriologically confirmed TB could be proposed to monitor contact investigation activities
- Implementation of procedures for TB diagnosis needs
  - Training of nurses and doctors
  - Simple and clear referral procedures
  - Standardized tools
- Use of chest X-Ray may be better restricted to symptomatic children
- 3 RH regimen is well tolerated and appears as effective as 6H in preventing TB in children, although results are still preliminary as post-treatment follow-up is not completed

# Thanks to all patients, families and children who participated in the study

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## Bénin

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## Burkina Faso

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## Central African Republic

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Edgar Djimbele  
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## Cameroun

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Adeline Wandji  
Edie Alain Kemenang  
Natacha Mbarga  
Ghislain Tchualak  
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Sarah M. Takoukam  
Marie-Nadège Manga  
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## The Union

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Valérie Schwoebel  
Kobto G. Koura  
Alberto Roggi  
Arnaud Trébucq

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## Scientific Committee

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Christophe Delacourt  
Anne Detjen  
Steve Graham  
Eric Masserey  
Philippe Msellati

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Initiative 5 Pour Cent



