




Performance of a clinical score for the diagnosis of *Mycobacterium ulcerans* infection in Akonolinga, Cameroon

WHO meeting on Buruli ulcer 2015

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Rationale

- Buruli ulcer (BU) mostly in rural areas with limited diagnostic means
 - Diagnosis often relies on clinical judgment
 - Imperfect performance of laboratory tests
 - Lack of gold standard
 - PCR?
 - Composite standard of one, or two, positive laboratory tests
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Main objective

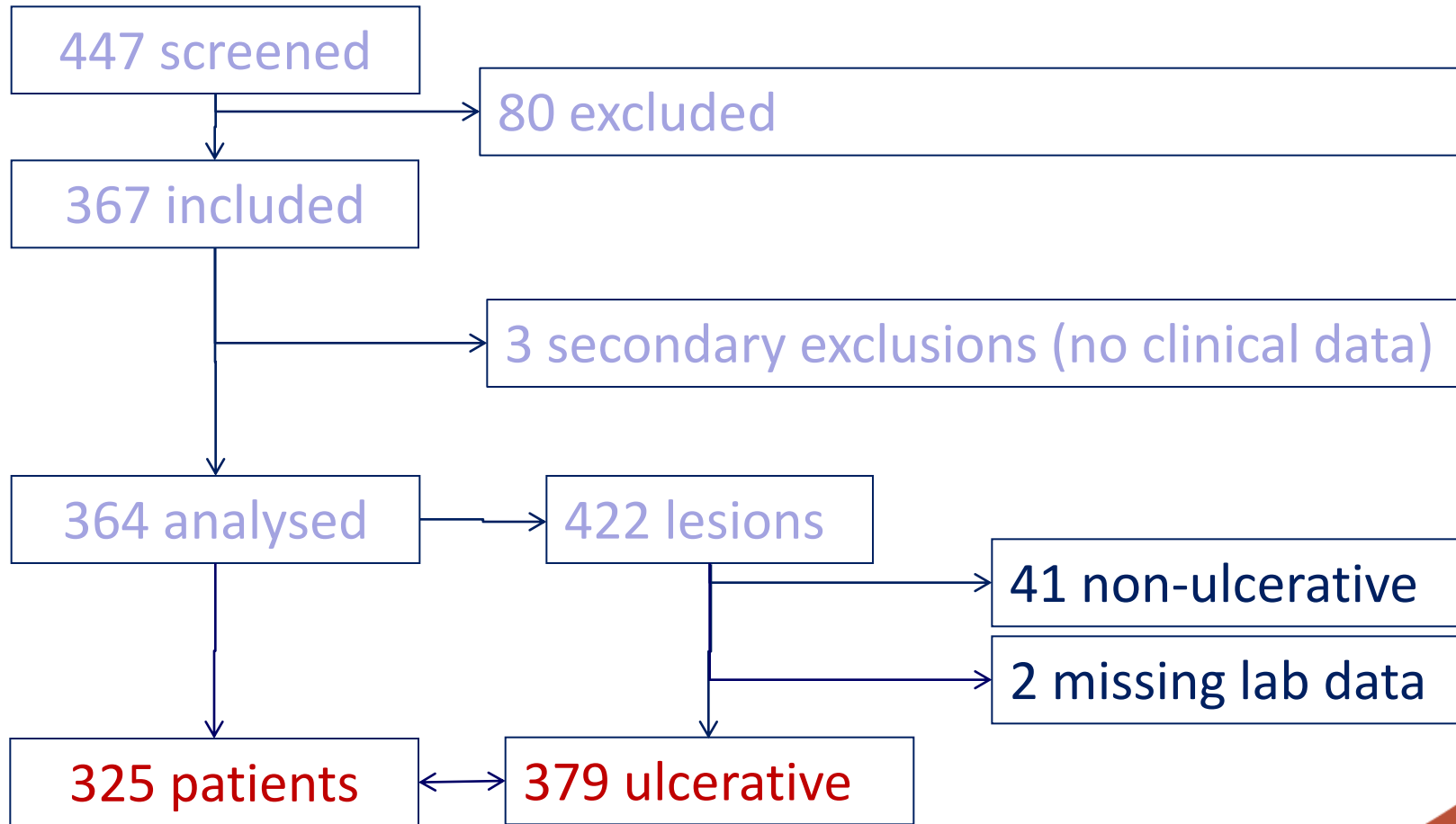
- To establish a score to support clinical decision making when a *Mycobacterium ulcerans* infection is suspected.
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Methods

- Latent class model with results of laboratory tests (2 ZN, PCR, culture)
 - Categorization of patients with high, respectively low BU probability
- Selection of variables in the score
 - Univariate analysis of variables associated with high BU probability (from LCA)
 - Variables associated with $p < 0.20$ included in multivariate model
 - Variables with $OR > 2.0$ or < 0.5 after adjustment included in score
 - Rounding off of coefficient
- Calculation of sensitivity, specificity and predictive values associated with each cut-off of the score
- Choice of final cut-off

RESULTS

Patient flow

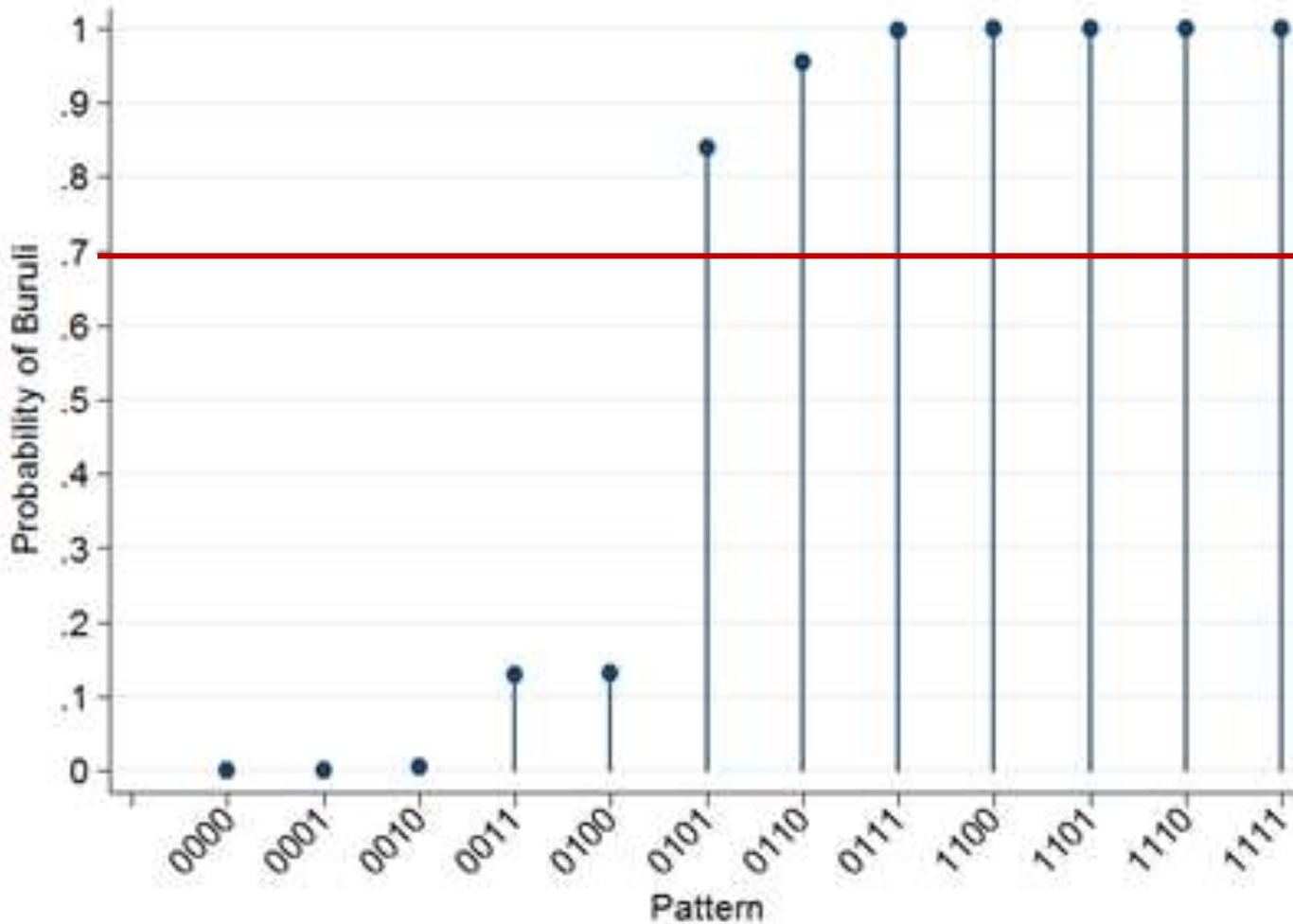


LCA:

Latent class model

BU prevalence	16.1	(12.4 – 20.7)		
	Sensitivity		Specificity	
ZN Akonolinga	0.72	(0.60,0.85)	0.93	(0.90,0.96)
ZN CPC	0.65	(0.51,0.80)	1.00	(1.00,1.00)
PCR	1.00	(0.97,1.00)	0.93	(0.89,0.96)
Culture	0.46	(0.33,0.59)	0.99	(0.98,1.00)

BU probability by pattern of test response



Predefined
treatment
threshold: 0.7

Univariate analysis		High BU prob (N=51)		Low BU prob (N=274)		p-value
Patient characteristics		n	%	n	%	
Age	Up to 20 years old	35	68.6	59	21.5	<0.001
	21 to 40 years old	10	19.6	76	27.7	
	Over 40 years old	6	11.8	139	50.7	
Gender	Male	25	49.0	187	68.3	0.008
	Female	26	51.0	87	31.8	
Median duration of episode (IQR)		8	4 - 28	28	5 - 108	<0.001
Abnormal vascular examination		3	5.9	67	24.5	0.003
Abnormal neurological examination		0	0.0	21	7.7	0.04
Previous topical treatment		28	54.9	183	66.8	0.102
Previous systemic treatment		27	52.9	196	71.5	0.009
History of trauma		13	25.5	104	38.0	0.089
Oedema	None	24	47.1	123	45.7	0.157
	Perilesional	21	41.2	80	29.7	
	Of the affected limb	6	11.8	56	20.8	
	Both lower limbs	0	0.0	10	3.7	

Univariate analysis		High MU prob (N=59)		Low MU prob (N=320)		p-value
Lesion characteristics		n	%	n	%	
Localisation						0.001
	Upper limb	13	22.0	22	6.9	
	Lower limb	42	71.2	280	87.5	
	Trunk	4	6.8	18	5.6	
Size	<=5 cm	33	55.9	128	40.0	0.075
	>5 to 15 cm	18	30.5	133	41.6	
	>15 cm	8	13.6	59	18.4	
Hyposensitivity		3	5.1	7	2.2	0.193
Induration		14	23.7	104	32.8	0.168
Adenopathy		7	11.9	82	25.6	0.022
Pain at rest		26	44.1	192	60.2	0.021
Undermining		37	62.7	96	30.0	<0.001
Characteristic smell		17	28.8	22	7.0	<0.001
Green (pus)		19	32.2	69	21.6	0.075
Yellow (fibrinous)		54	91.5	242	75.6	0.007
Red (bourgeoning)		41	69.6	268	83.8	0.010

Variables NOT associated with BU (univariate analysis)

- HIV
- History of fever
- Number of lesions
- BU cases in the vicinity
- Side of the lesion
- Traditional treatment
- Depth of the lesion
- Suspicion of bone involvement
- Complication
- Warmth
- Local prurigo
- Pain during dressing
- Lesion edges
- Exsudate quantity
- Exsudate quality
- Black color
- Pink color

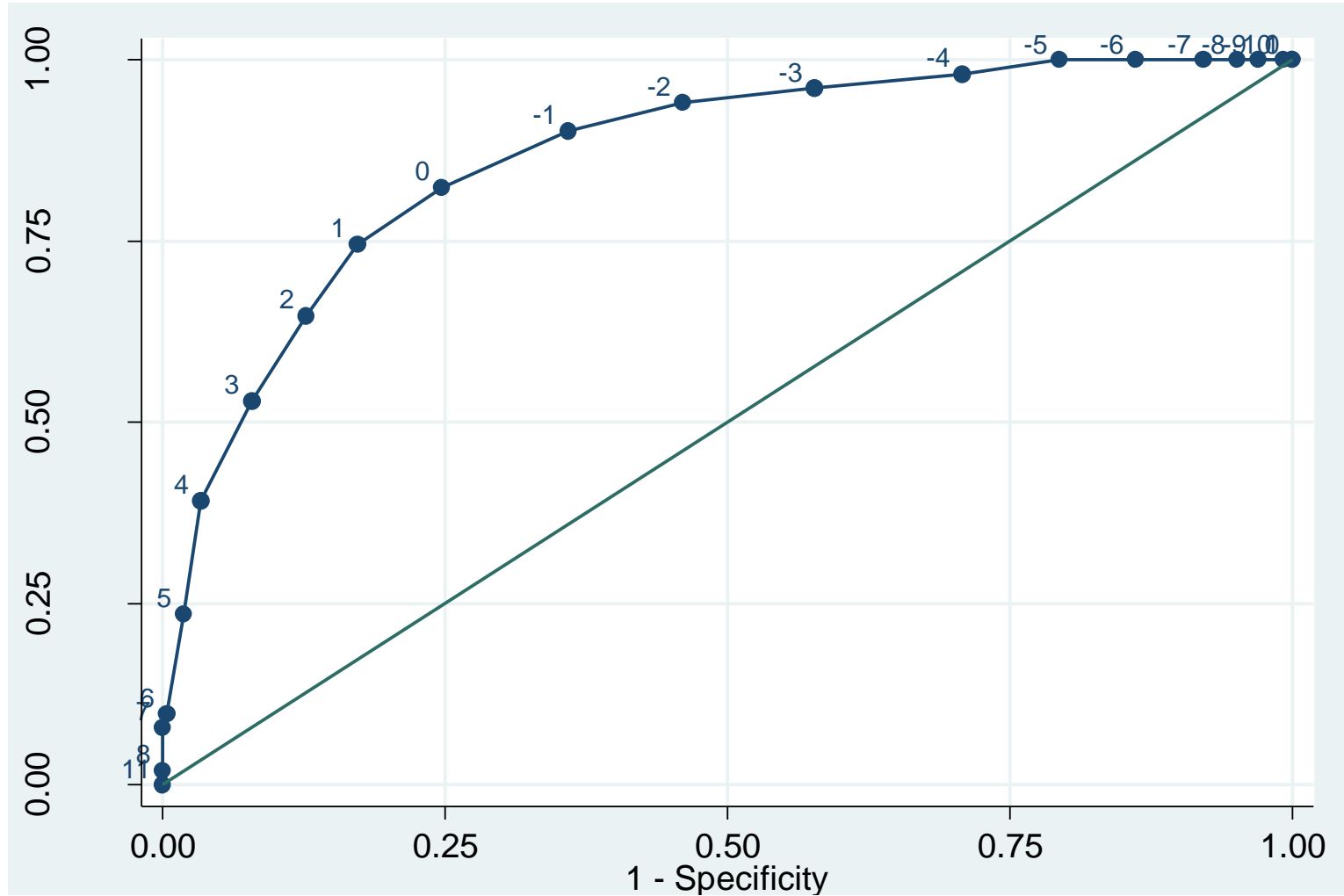
Selection of variables for score

- $OR > 2.0$ or < 0.5
- Variables dropped: duration of episode, topical or systemic treatment, history of trauma, vascular anomaly, history of fever, red color, black color, green color, localization of the lesion, induration, type of oedema, undermining, pain at rest, lesion size

Buruli score (short version)

Buruli score	Points	
Characteristic smell	+3	
Yellow color (fibrin)	+3	
Lesion hyposensitivity	+2	
Female	+2	
Abnormal neurological examination		-10
Age above 20 and up to 40		-3
Age above 40 years		-5
Locoregional adenopathy		-2

ROC curve



Final model AUC 0.87 (95%CI 0.82 – 0.90)

Other score (long version)

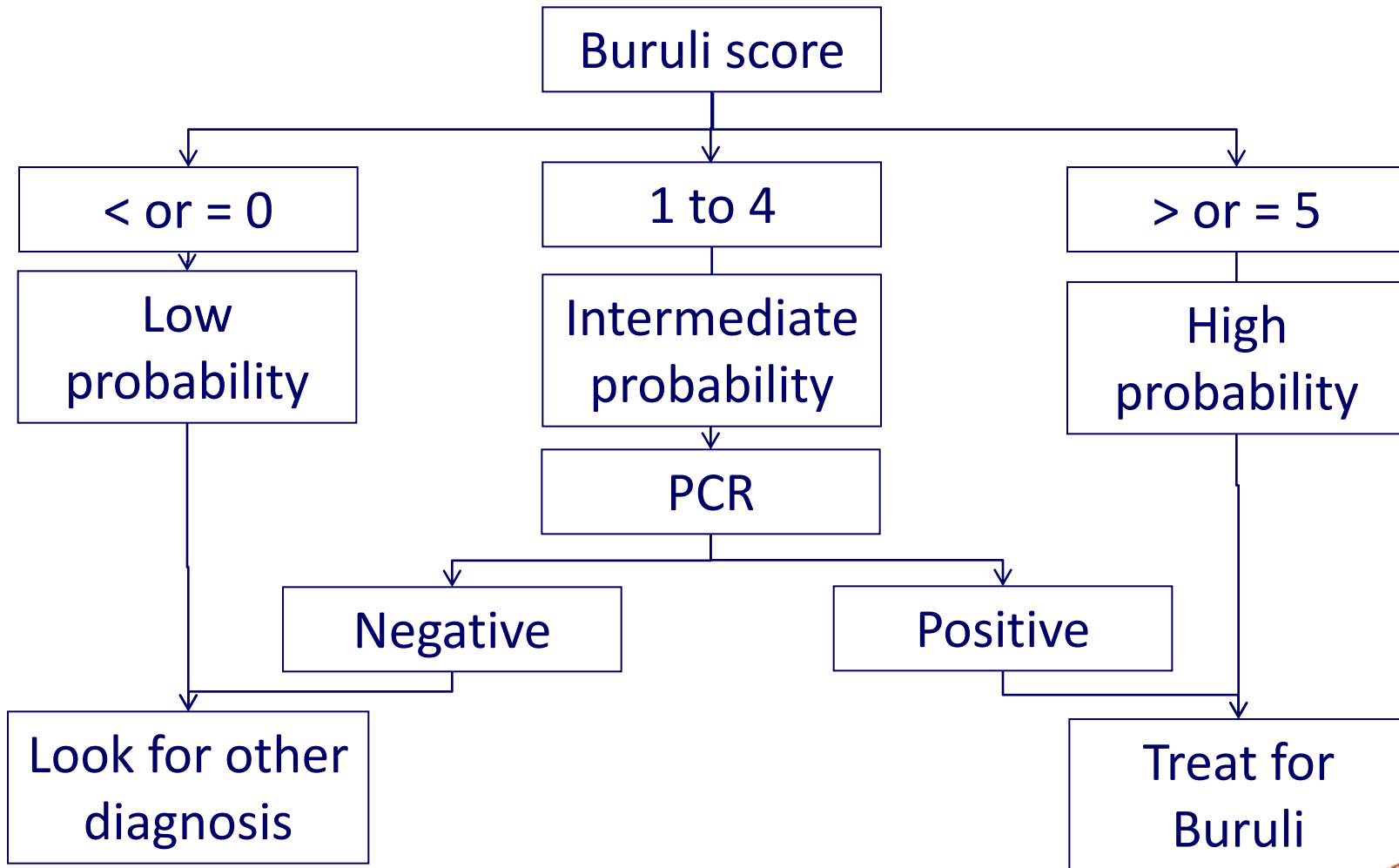
- Keeping variables with OR>1.5 or <0.67
- Similar AUC compared to short score
- No difference in terms of patient classification

Buruli score	Points	
Characteristic smell	+3	
Yellow color (fibrin)	+3	
Female	+2	
Lesion hyposensitivity	+2	
Undermining	+1	
Green color	+1	
Neurological anomalies		-10
Age above 20 and below 40		-3
Age above 40 years		-5
Adenopathy		-2
Pain at rest		-1
Lesion size > 5cm		-1

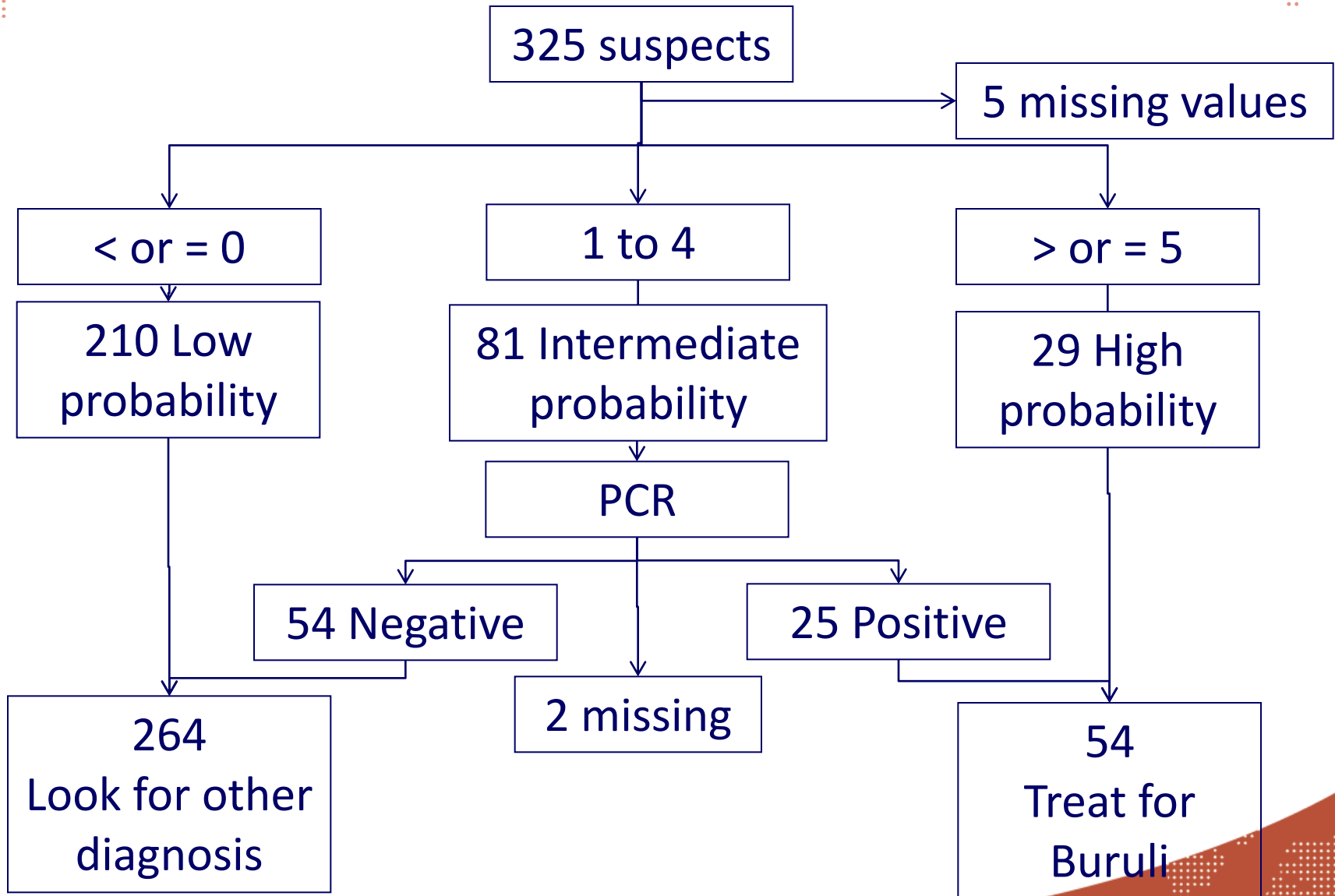
Definition of cut-offs

- To exclude BU: negative predictive value >95% (95CI>90%)
 - Score ≤ 0 : NPV 95.7% (95CI 92.0 – 98.0)
- To treat BU: positive predictive value >70%
 - Large CI!
 - Score ≥ 5 : PPV 69.0% (95%CI 49.2 – 84.7)
 - Score ≥ 6 : PPV 70.6% (95%CI 44.0 – 89.7)

Buruli algorithm



Applied to study patients



Comparison between algorithm and latent class model

	Algorithm			Score performance	
BU probability (LCA)	BU (N=54)	Not BU (N=264)	Total (N=318)	Sensitivity	Specificity
High	42	9	51	82.4% (69.1 – 91.6)	
Low	12	255	267		95.5% (92.3 – 97.7)
	PPV: 77.8%	NPV: 96.6%			


Comparison with laboratory tests

	Sensitivity (95CI)		Specificity (95CI)	
Algorithm	0.82	(0.69,0.92)	0.96	(0.92,0.98)

	Sensitivity (95CI)		Specificity (95CI)	
ZN Ako	0.72	(0.60,0.85)	0.93	(0.90,0.96)
ZN CPC	0.65	(0.51,0.80)	1	(1.00,1.00)
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Discussion

- Algorithm based on Buruli score
 - Four times less PCR
 - Sensitivity not perfect (82%), but high NPV (97%)
 - Low BU prevalence in our study
 - Can miss some true Buruli cases
 - Clinicians to reevaluate patient if does not respond well to treatment of non-BU
- 




Discussion

- Performance in other contexts?
 - Very dependent on age and sex
 - Depends on patient selection (BU prevalence)
 - Quality of clinical examination
 - Adenopathy, neurological examination
 - Subjectivity of some parameters in the score
 - Hyposensitivity, smell, undermining, color
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Limitations

- Latent class based on laboratory results
 - Patients with no positive test not considered BU
 - Independence between tests not perfect
 - Not very precise definition of BU suspect, shift of patient population during study
 - Not sufficient data for non-ulcerative lesions
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Perspectives

- External validation on external dataset
 - Implementation – validation in Cameroon
 - Sites: Ayos, Akonolinga and Bankim
 - Objectives
 - Reproducibility of the score
 - Performance by non-doctors
 - Impact on delay to treatment, loss-to follow-up
 - Cost-effectiveness?
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Acknowledgments

- Study participants
- Staff of Akonolinga District Hospital and Health Centres
- National Program for Buruli Ulcer Control
 - **Earnest Njih Tabah**
- Doctors without borders
 - **Patrick Nkemenang, Geneviève Ehounou, Eric Comte**, Marie Tchaton, Dominique Charleux, Alain Georges Nkama, Franc Eric Wanda Djofang, Alain Kamdem, Cédric Sidi Tchameni, Serge Maturin Kaboré, Colince Fosso Mba
 - MSF team in Akonolinga and Yaounde
- Epicentre
 - **Mathieu Bastard, Jean-François Etard**, Fabienne Nackers, Clotilde Rambaud-Althaus
- Centre Pasteur Cameroon
 - Yannick Kamdem, Sara Eyangoh, Paul Atangana
- Central Hospital, Yaounde
 - **Didier Junior Mboua**
- Geneva University Hospitals
 - **Laurence Trelu Toutous**, Isabelle Masouyé, Yasmine Lucile Ibrahim, Elizabeth Tchanz, Damjan Nikolic, Hubert Vuagnat
- Hopitaux civils de Lyon
 - Muriel Rabilloud
- Fondation Raoul Follereau, Benin
 - Annick Chauty, Roch Christian Johnson



Marcel Nimfuehr, MSF

