nidiag

Better Diagnosis of Neglected Infectious Diseases

The role of RDTs in improving the clinical management of patients presenting with Neurological Syndrome

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NIDIAG approach

the problem

- Neurologic infections common/severe in LRS
- Important cause of hospital admission in rural Africa (10%)

WHO. Global Burden of Disease. 2004
*Int J Infect Dis **2007** Nov;11(6):524-30*

- Numerous “severe and treatable” diseases
- Early Dx & Rx improve outcomes

*Emerg Infect Dis **2007** Jun;13(6):883-8.*
*Clin Infect Dis **2004** Nov 1;39(9):1267-84.*

Epidemiology of Neurological neglected infectious diseases in Central Africa

Pathology	DRC Incidence / prevalence	Comment
Human African trypanosomiasis (HAT) [*T.b. gambiense*]	• 8,162 cases **reported 2007** (~13.0/100,000*yr) • 18,592 **estimated 2007*** (29.7/100,000*yr) • 5,500 cases **reported 2010** (~8.8/100,000*yr)	• ↓ incidence since peak in 1998 • 70% of global burden in DRC • 50% stage 2 • 50% detected in mass screening • *[95%CI 4,883–32,302]
Cysticercosis	?	• *Human dz detected in Bas-Congo* • *Porcine dz elsewhere*
Schistosomiasis	?	• Neuro in 2-4% *S. mansoni* infections • Last DRC survey pre-1980s: www.who.int/schistosomiasis/Global-Atlas • 3 species know to exist in DRC • Eggs rarely seen in labs we surveyed
Rabies	?	• Several recent outbreaks (p-comm) • No PEP available
Leprosy	Prevalence <10 / 100,000 2007	• “Elimination” threshold reached in 2007

Pathology	DRC Incidence/prevalence	Comment
Malaria	**Adult parasitemia PCR:** **DRC = 33.5%** **Bandundu >>50%**	• **2007 Data (*PLoS One 2011;6(1):e16420)*** • **RDT used x 2011** • **M.A.F. / clinical specificity unknown** • **Neuro dz in adults probably rare**
HIV infection	**1.3% national prev.** **4.3% pregnant women**	• **No data on OI prevalence**
TB	**390 / 100,000*yr** **CNS - ?**	• **~1% case with TBM estimated** • **~Never diagnosed in sites visited**
Cryptococcal meningitis	**?**	• **CrAg apparently unavailable** • **India Ink rarely done**
Bacterial meningo-enceph.	**?**	
Viral meningo-encephalitis	**?**	
Syphilis	**RPR positivity:** **~1% blood banks screen** **2-3% antenatal screen**	• **CNS involvement unknown** • **~never diagnosed**

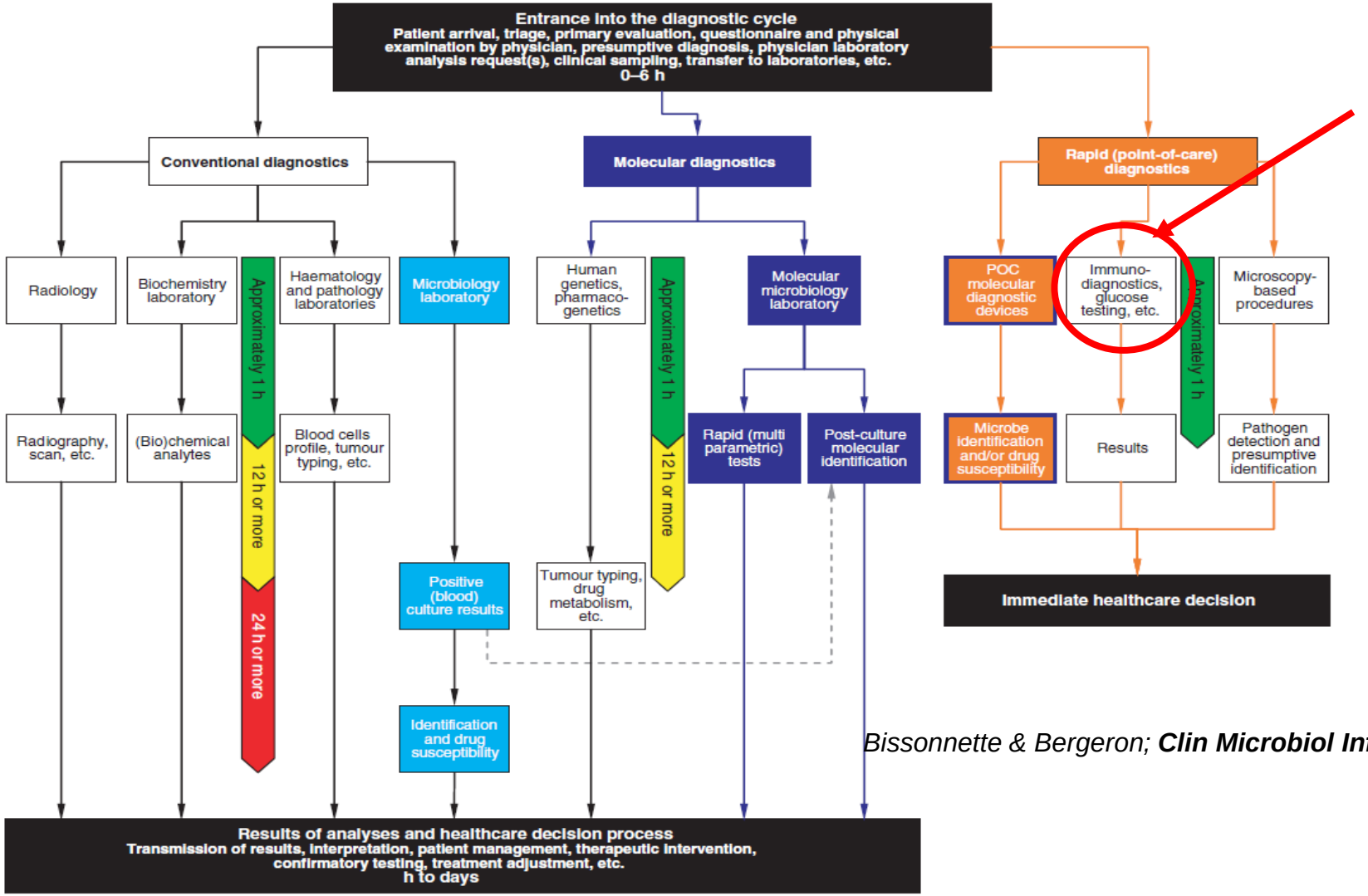
Key pathogens to target

Targeted : differential dx, expected prevalence, severe &treatable, no imaging for treatment decision

Pathology	RDT for ≥phase3 ?	Comment
HAT stage 2	Yes*	• Single format serology test only
Cerebral malaria	Yes**	• Fully validated RDTs already in use • *Clinical specificity for neuro unknown and likely LOW*
HIV infection (1ry and associated disorders)	Yes**	• Fully validated RDTs already in use • Performance affected by HAT!
TB meningitis	No*	• Combo ADA/IFN-g/LAM RDT in pipeline • Handheld RT-PCR
Cryptococcal meningitis	Yes	• IMMY CrAg LFA
Bacterial meningitis	Yes/No***	• Single pathogen tests w/variable performance
Neurosyphilis	Yes**	• Fully validated RDTs already in use • *Clinical specificity for neuro unknown and likely LOW*

Pathology	RDT for ≥phase3 ?	Comment
Neurocysticercosis	No**	Imaging needed for treatment decisions
Toxoplasmosis*	No**	Imaging required for phase 3 evaluation of any RDT as part of composite reference standard – *not possible in DRC*
Helminthic encephalitis	No	Imaging needed for treatment decisions
Rabies	No	No treatment
HTLV-1	No	No treatment
HSV-1*	No	Good candidate for LAMP assay

What are we talking about, exactly?



Bissonnette & Bergeron; ***Clin Microbiol Infect 2010***

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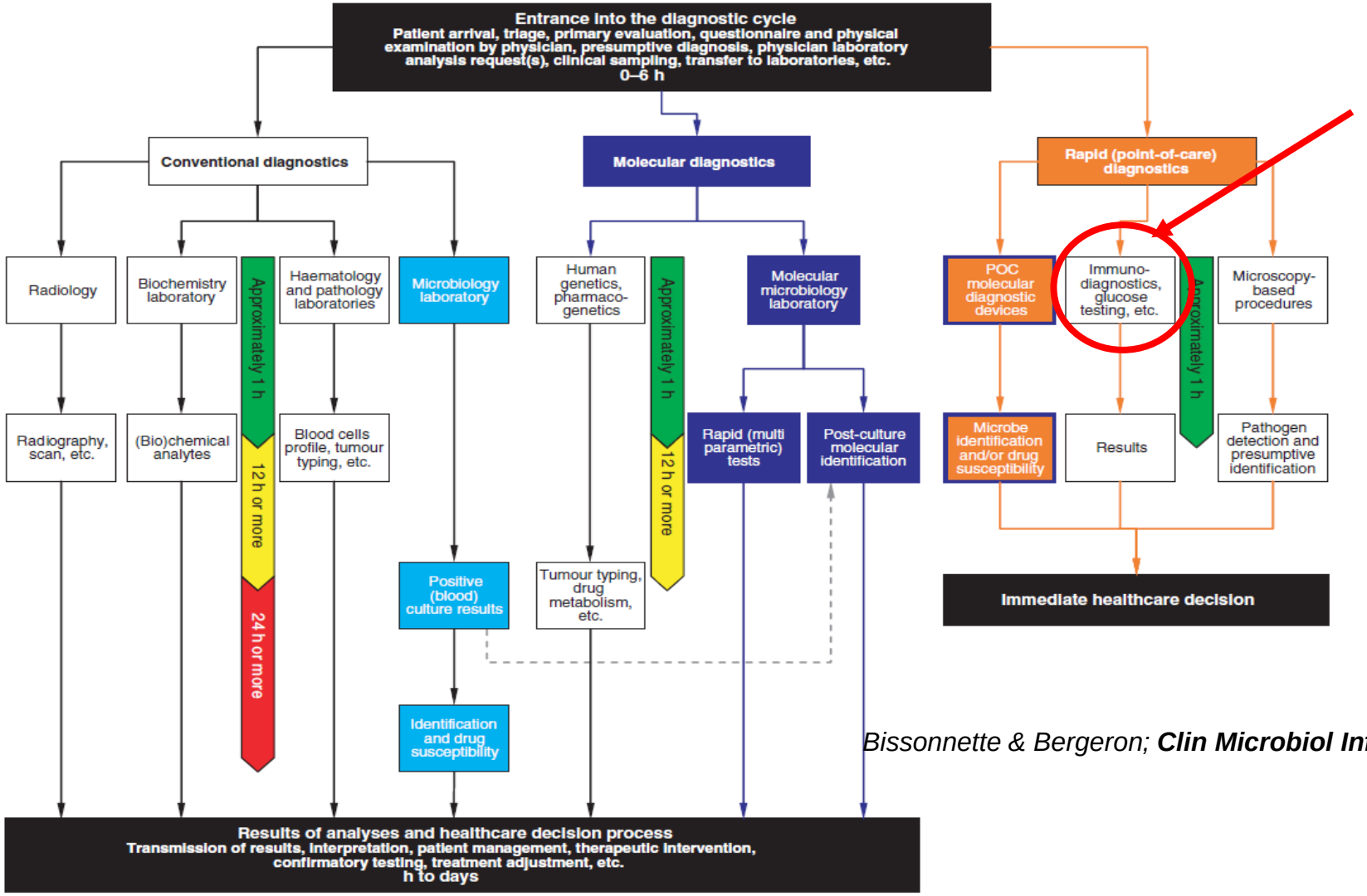
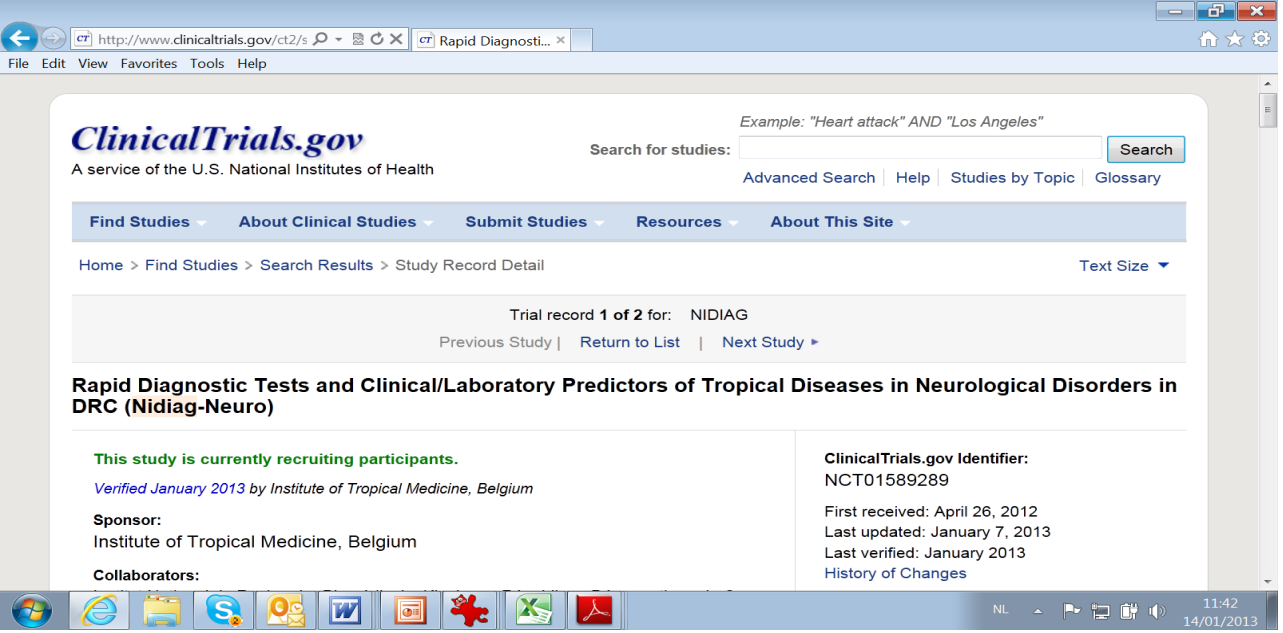


Bissonnette & Bergeron; ***Clin Microbiol Infect 2010***

Rapid diagnostic tests for neurological infection in central Africa. Lancet Infect Dis. 2013;13(6):546-58

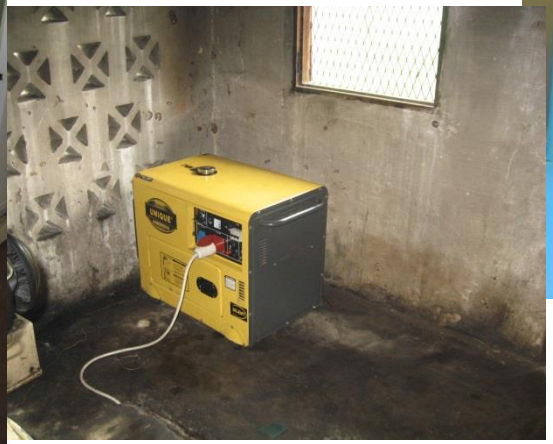
Study performed in Mosango, rural part of DR Congo



Inclusions from Sep 2012 to Jun 2014

Follow-up until Dec 2014


LEPROSERIE
& M.I.F.
SANATORIUM
& M.I.H.

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reference standards

Pathology	NIDIAG reference standard
HAT stage 2	demonstration of trypanosome in any sample (blood, lymph node, cerebrospinal fluid [CSF]) with concentration methods, and consistent CSF abnormalities (on sites)
Cerebral malaria	WHO 2000 case definition, with microscopy and Plasmodium identification/quantification (on sites)
HIV infection	3-step RDT strategy (Determine; Unigold; Double Check)
TB meningitis	Uniform case definition from Marais (TLID 2010) (“definite” AND “probable”; TB culture and molecular testing at INRB, Kinshasa).
Cryptococcal meningitis	Positive results from any of the following: India ink, Cryptococcal Ag latex agglutination, or Cultures of blood or CSF
Bacterial meningitis	Bacterial culture of CSF or blood (INRB, Kinshasa); positive CSF Gram stains and when negative cultures
Neurosyphilis	Rapid Plasma Reagin (RPR) and Treponema pallidum particle agglutination (TPPA) tests on serum; Veneral (VDRL) test on CSF

reference standards

selected post-hoc testing

- Serology for *T. solium*, *Schistosoma spp*, *Brucella spp* and T*. gondii* (the latter only for HIV)
- Antigenic test for *T. solium*
- Nucleic acid amplification on CSF for *Herpes simplex/Herpes zoster* and *Mycobacterium tuberculosis*

Lancet Infect Dis. 2013;13(6):546-58.

NIDIAG neuro study: baseline characteristics

- Inclusions: 351
- Mean age: 39 years (children under five were excluded)
- Sex ratio M/F: 1.17
- Previous contact with health care system: 45.6%
- Exposure
  - To antibiotics: 92 (26%)
  - To antimalarials: 79 (22%)

NIDIAG neuro study: main presenting symptoms (n=351)

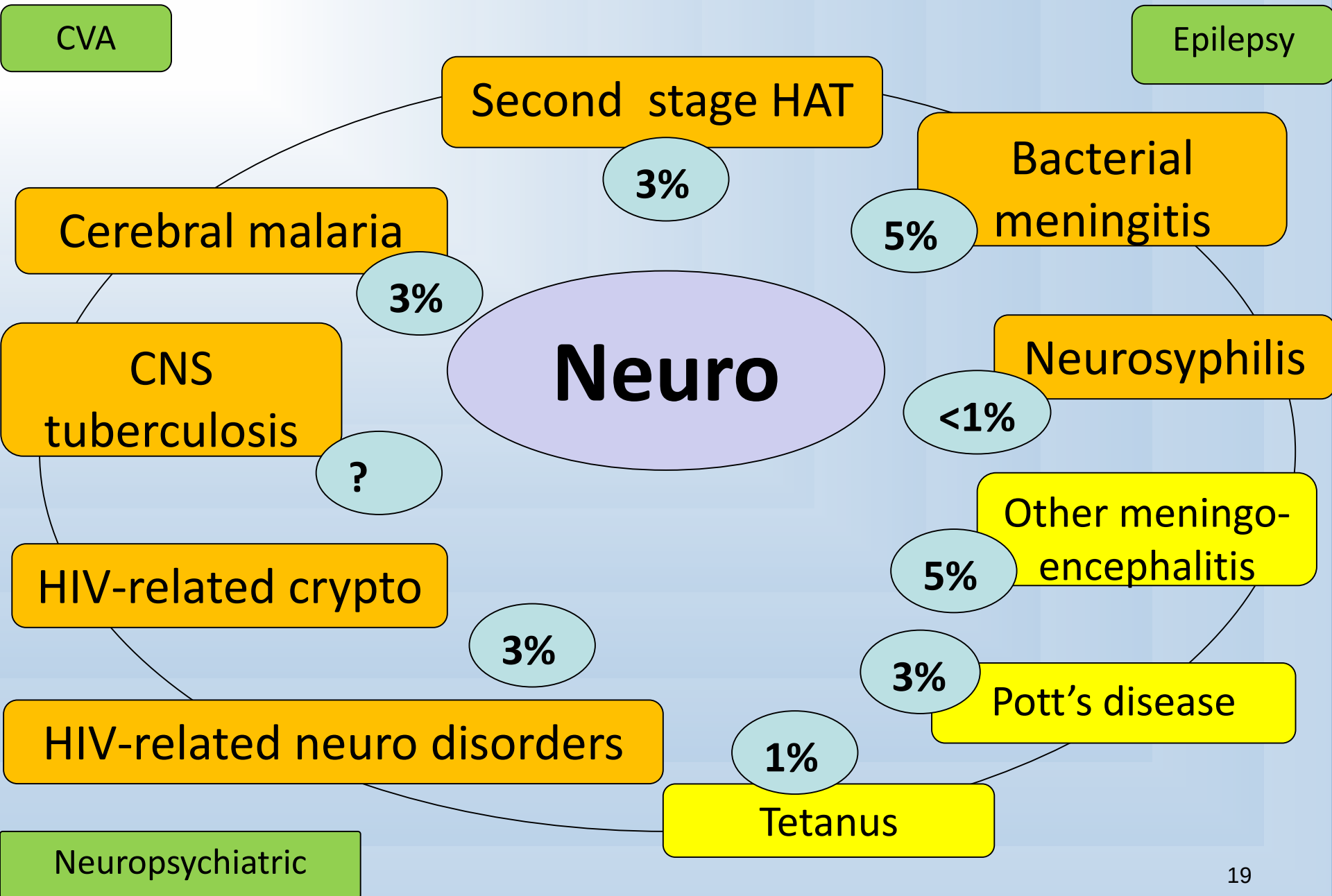
Entry criteria	n	%
Severe daily headache	160	45.7
Meningismus	111	31.7
Walking disturbances	97	27.7
Recent convulsion	87	24.9
Sensitivo-motor deficit	77	22.0
Behaviour disturbances	66	18.9
Altered consciousness	54	15.4
Sleep disturbances	51	14.6
Cranial nerve lesions	19	5.4
Cognitive decline	18	5.1

NIDIAG neuro study: main diagnoses (at admission and reviewed by panel of experts (n=351)

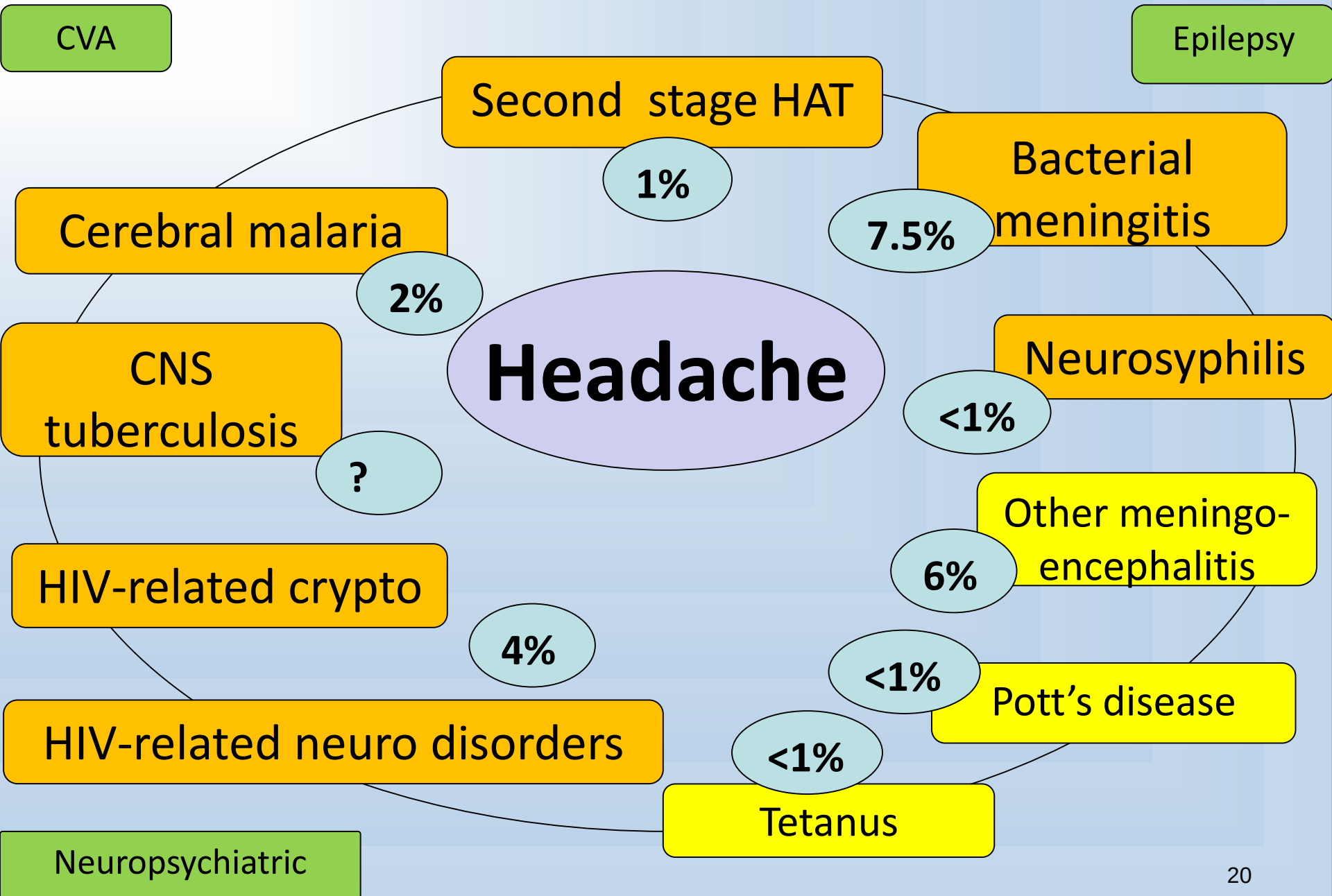
	n	%
“Idiopathic” epilepsy	58	16.5
Neuropsychiatric disorders	54	15.4
Priority infections (7)	48	13.7
Other infections	47	13.6
Cerebrovascular accident	22	6.3
Otitis/sinusitis	18	5.1
Myelopathy	10	2.9

NB: To consider as lowest numbers; still unknowns 58/351 (16.5%)

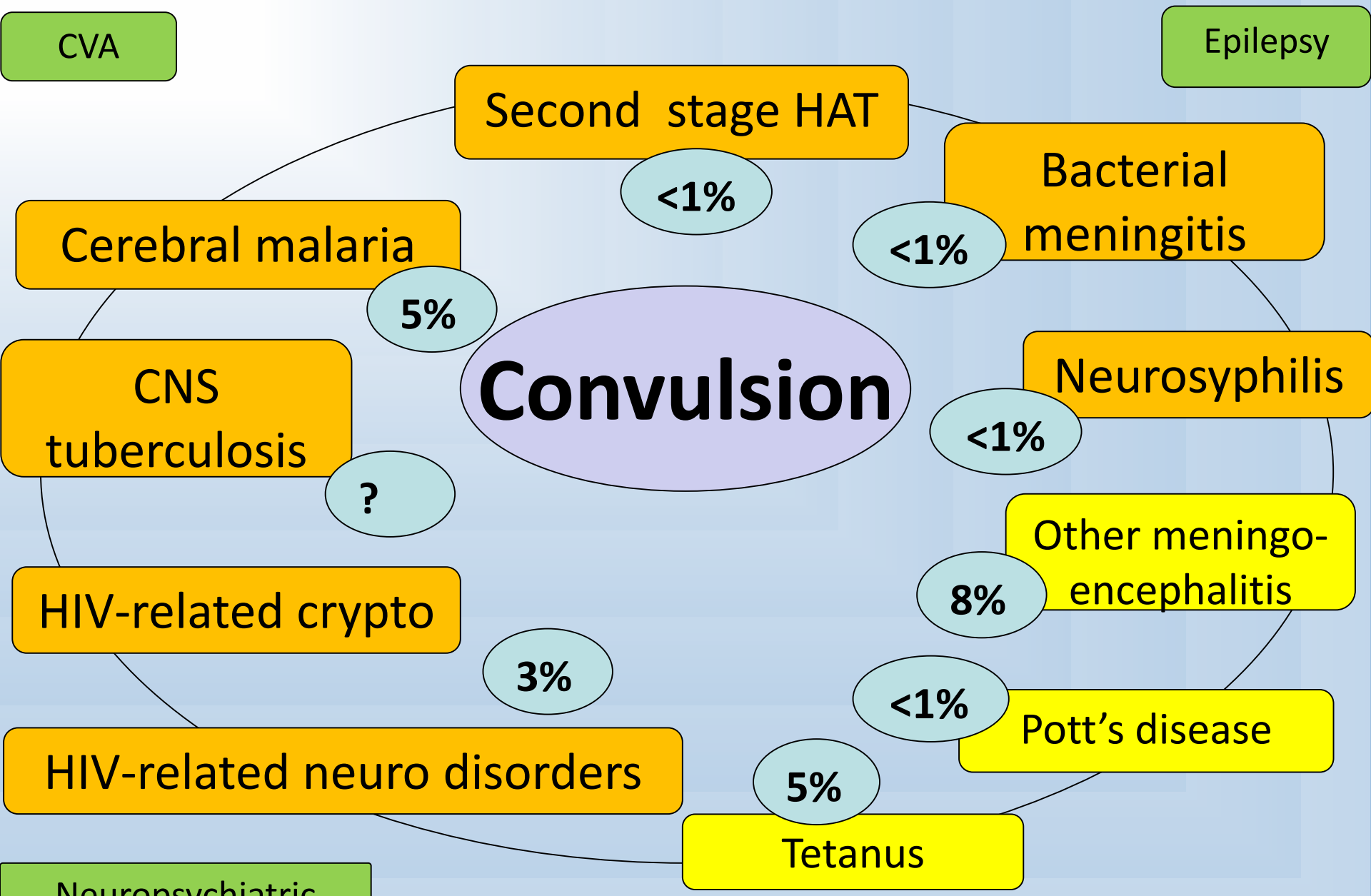
“Neuro syndrome” (n=351): pre-test probabilities



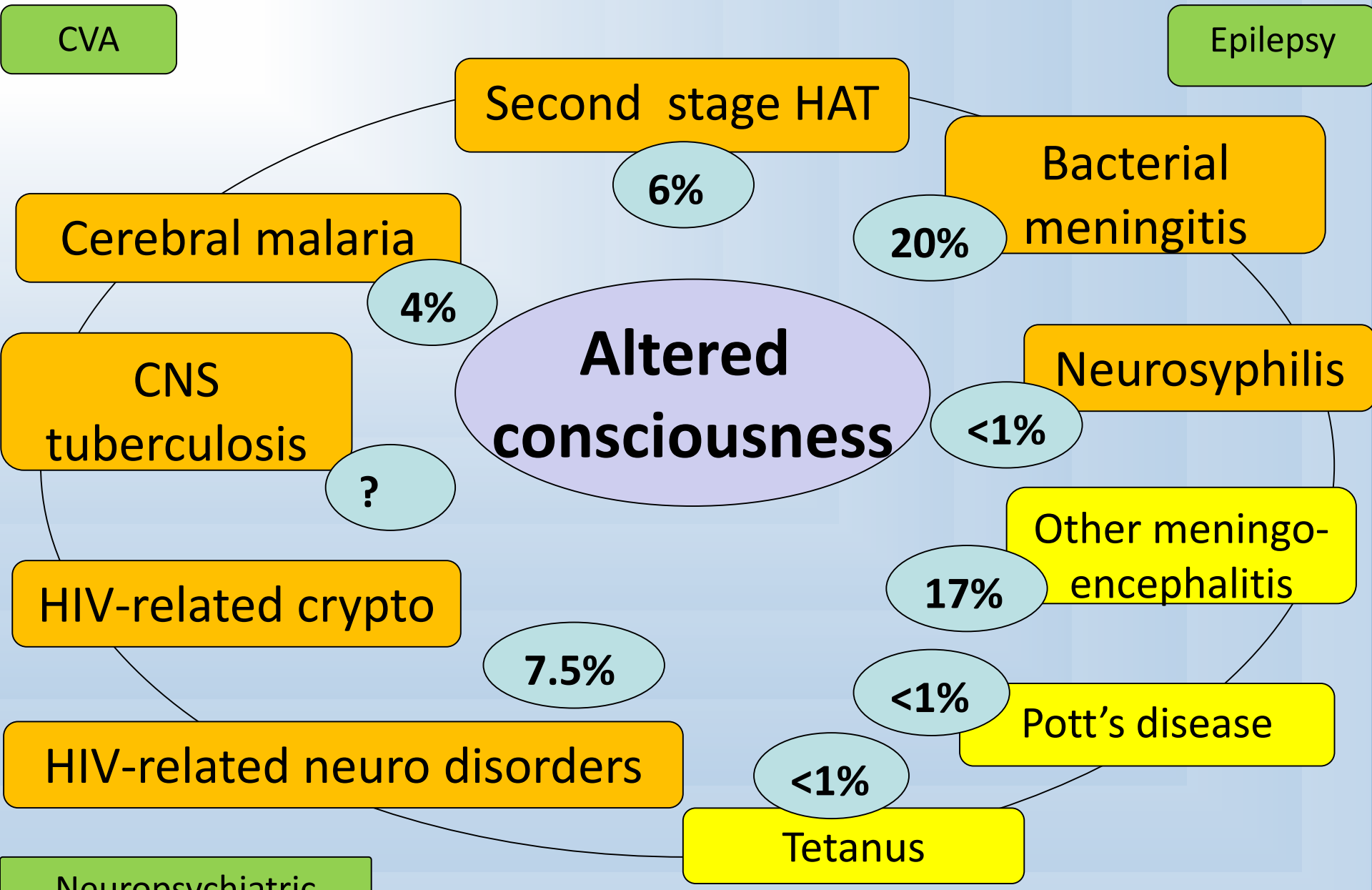
Severe headache (n=160): pre-test probabilities



Convulsion (n=87): pre-test probabilities

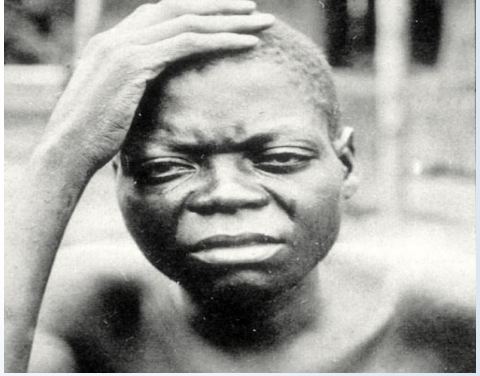


Altered consciousness (n=54): pre-test probabilities



Performances of RDTs: preliminary results

	Sensitivity	Specificity
CATT whole blood	*10 (100%)*	*9 (2.7%)*
HAT-RDT Coris	*10 (100%)*	*9 (2.7%)*
Malaria RDT HRP2/pLDH	*10 (100%)*	*92%*
Malaria RDT pf-pan/LDH	*10 (100%)*	*99%*
HIV RDT Determine	*11 (100%)*	*92%*
Crypto RDT in CSF	*11(100%)*	*99%*



Headache

Certain

Probable

Possible

Impossible

Probability of HAT stage 2

"Prediction is difficult, especially about the future"

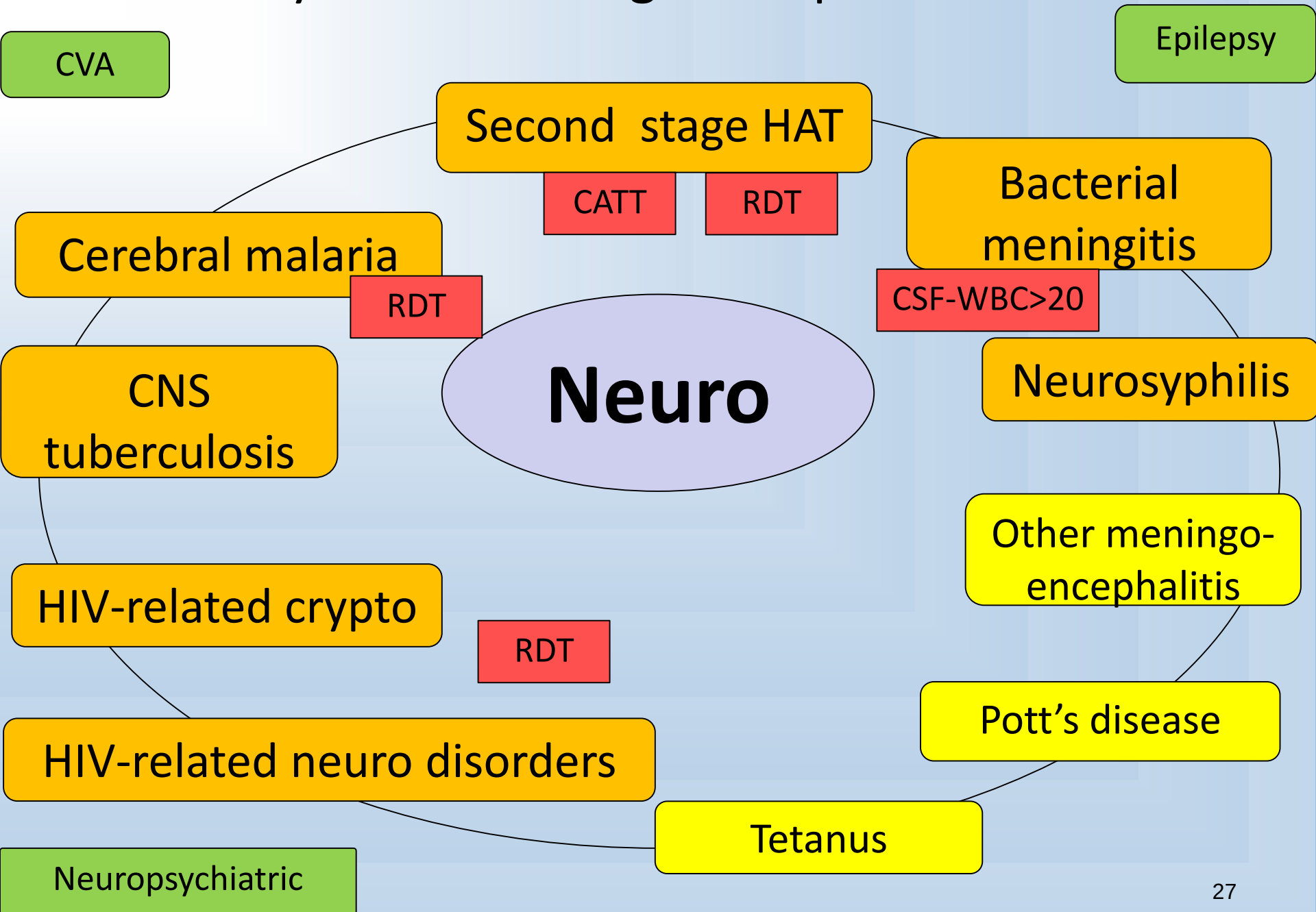
Diagnostic predictors (clinical signs and lab tests including RDTs) and LR+/LR-

- Identification of features associated with each priority diagnosis
- Calculation of LR+/LR- according to standard formulas
- Features with LR+
  - around 3: weak predictor
  - around 10: good predictor
  - around 33: strong predictor
  - around 100: very strong predictor (diagnostic tests)

Diagnostic predictors neuro study

Confirmers	HAT			Bacterial meningitis			(Cerebral) malaria			HIV		
Excluders	Frequency (%)	LR+	LR-	frequency (%)	LR+	LR-	frequency (%)	LR+	LR-	frequency	LR+	LR-
Sleep disorders	60	4,5										
Daily hypersomnia	30	7,3										
Behaviour disturbances	60	3,3										
Fever < 7 days				75	8,5	0,3	30	2,8				
Fever > 7 days										36	6,2	
Nausea/vomiting				50	15,6		30	3				
Dysphagia	22	5,8										
Diplopia	33	17										
Cough										27	3,5	
Altered consciousness				75	5,7		22	4,9		36	2,5	
Rooting reflex	50	8,5										
Palmo-mentar reflex	40	6,8										
Tongue movements	25	15,9										
Nose-finger test	50	5,9										
Neck pain				80	2,5	0,3						
Neck stiffness				93	2	0,13						
Splenomegaly	20	34										
Localized lymph node	20	4										
Localized edema	33	17										
Rash				25	7,5							
CATT full blood	100	38	0									
HAT-RDT Sero-K-set	100	36	0									
CSF - WBC > 20	90	10	0,11	92	12,5	0,07				36	3,5	
CSF - WBC > 5	100	7	0	100	7,2	0				63	3,9	
CSF-Gram stain				80	33	0,21						
Malaria RDT pf/pan LDH							100	100	0			
Malaria RDT pLDH/HRP2							100	14	0			

“Neuro syndrome”: diagnostic panorama



Possible guidelines for neurogical neglected infectious diseases in rural context with limited resources

Patients with neurological disorders: initial diagnostic work-up

Applies to patients with:

V
- Altered consciousness
- Severe increasing headache
- Sleeping disorder
- Convulsions
- Focal neurological deficit

Does not apply to patients with:

X
- Trauma
- Convulsions since childhood
- Sequelae previous disease
- Age under five years

Rapid diagnostic tests:

- HIV
- Human African tryp.
- Malaria

Clinical exam:

- Vital signs
- Cervical lymph nodes
- Signs of AIDS
- Spleen
- Ear (otitis, mastoiditis)

Neurological exam:

- Mental status
- Cranial nerves
- Motor system
- Sensation
- Reflexes

Do lumbar puncture if:

V
- Altered consciousness or
- Fever or
- Neck stiffness or
- RDT positive for HIV or
- RDT positive for HAT

Do not do lumbar puncture if:

X
- A or
- B or
- C

Patients with neurological disorders: diagnostic panorama

Applies to patients with:

V

- Altered consciousness
- Severe increasing headache
- Sleeping disorder
- Convulsions
- Focal neurological deficit

Does not apply to patients with:

X

- Trauma
- Longstanding convulsions
- Sequelae previous disease
- Age under five years

Acute meningoenceph.

CSF Gram pos
CSF WBC >20
Nausea/vom.
Fever

CSF WBC nl

HIV – opportunistic inf.

RDT HIV pos
RDT cryp pos
Fever

RDT HIV neg

Cerebral malaria

RDT pf/pan +
Bbbbbb
Fever
Ddddddd

RDT pf/pan -

Human African tryp.

RDT/CATT +
Splenomeg.
Diplopia
Loc. oedema

RDT/CATT –
CSF WBC nl

Tetanus

Aaaaaa
Bbbbbb
Ccccccccc
Ddddddd

Aaaaaa
Bbbbbb
Ccccccccc
Ddddddd

Pott's disease

Aaaaaa
Bbbbbb
Ccccccccc
Ddddddd

Aaaaaa
Bbbbbb
Ccccccccc
Ddddddd

Neurosyphilis

RDT pos
Bbbbbb
Ccccccccc
Ddddddd

RDT neg
Bbbbbb
Ccccccccc
Ddddddd

Discussion, conclusion and recommendations

Limitations in our study
Targeted conditions: clinical/laboratory features

- low numbers for each priority infection
  - Frequency of symptom/sensitivity of diagnostic tests with large confidence intervals
  - Need to compare to larger case series published in the literature
    - Limited data
    - Cohorts rather different
    - Mechanism of “correction” ?
- In contrast good data on specificity
  - mirroring the frequency of a given symptom in all other diagnoses, in other words the false positives

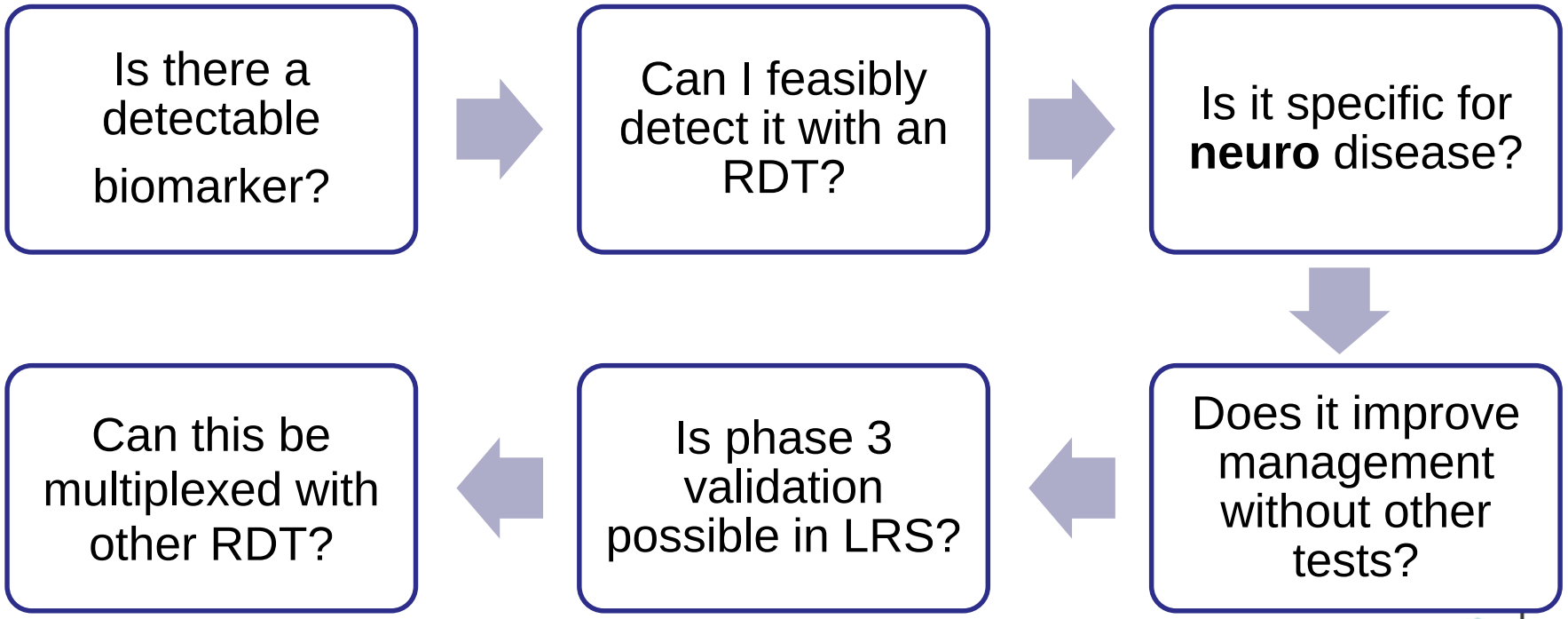
Conclusions

- About 15% of neurological disorders were due to the priority conditions, and up to 30% due to infections
- HAT stage 2, bacterial meningitis, malaria and HIV were diagnosed each in 1 to 5% of the neurological disorders, with frequencies varying according to the presenting symptom
- Several diagnostic predictors were identified, with some RDTs being the strongest ones for the respective diseases
- It is possible to improve diagnostic (early diagnostic) of neurological infectious diseases in LRS by adding RDTs to guidelines.

Recommendation for RDTs

Future validation of upcoming RDTs:
Opportunity for validation of RDTs for neurological syndrome: availability of samples well stored and well documented clinically.

Suggested scheme



Thank you for your attention