Performance of diagnostic algorithms based on Rapid Diagnostic Tests to detect Sleeping Sickness in DR Congo

5thJOINT EANETT/HAT PLATFORM SCIENTIFIC MEETING

"Research and control activities challenges in keeping HAT below the elimination threshold beyond 2020"

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Background

- The prevalence of *Tbg* HAT has fallen
  - HAT is targeted for elimination as PHP by 2020
  - At low prevalence, cost-effectiveness of active case detection decreases
  - Therefore integration of case finding into routine activities of peripheral health centres (PHC) becomes crucial.
  - Adapted diagnostic tests and test algorithms required
- Opportunities for an effective integration into routine activities of PHC:
  - The venue of individual rapid diagnostic tests (RDT) for of HAT screening:
    - ✓ 1st generation RDT (native antigens): HAT Sero-*K*-set, SD Bioline HAT 1.0
    - ✓ 2nd generation RDT (recombinant antigens): rHAT Sero Strip, SD Bioline HAT 2.0
  - Serological (Trypanolysis, ELISA) and molecular (LAMP, RT-PCR) reference tests (RT) performed at national/regional reference centres

Objectives

General objective:

- To validate the performance of diagnostic tools and algorithms for diagnosis of *Tbg* HAT under conditions of passive case detection

Specific objectives :

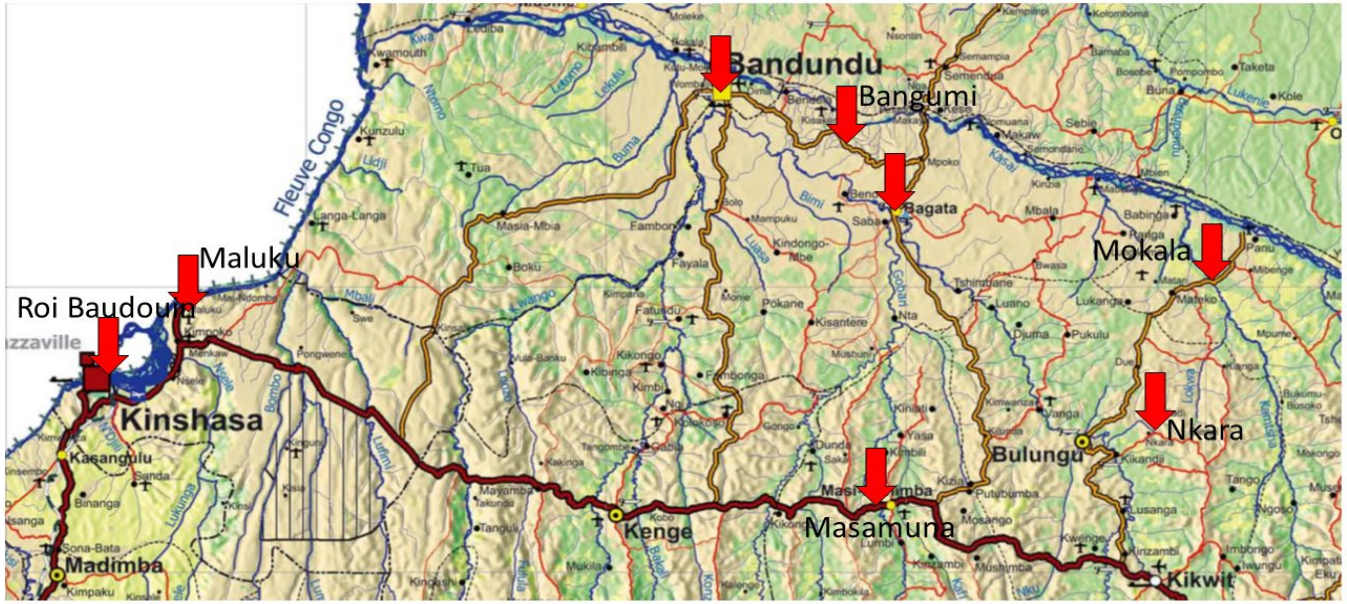
- To determine the diagnostic performance and costs for passive case detection in PHC in low prevalence HAT foci of:
  - HAT rapid diagnostic tests (RDT) performed on clinical suspects using fresh blood
  - combinations of HAT RDTs performed on clinical suspects using fresh blood
  - diagnostic algorithms of HAT RDTs on clinical suspects using fresh blood, with serological and/or molecular reference tests (RT) on filter paper (FP) at regional reference centres (INRB, Kinshasa, DR Congo)

Methodology - general

- This work in DR Congo is part of the DiTECT-HAT project
- Study Setting: Two levels of health centres
  - Serological Screening Sites (SSS) : Clinical suspicion, perfom RDT, refer RDT+ve to CDT
  - Centres for Diagnosis and Treatment (CDT) : clinical suspicion, perform RDTs and parasitological confirmation of HAT, and treat HAT. Use of electronic case report forms.
- Inclusion criteria: Clinical suspicion of HAT
- Exclusion criteria
  - Previously treated for HAT
  - No informed consent
  - < 4 years old

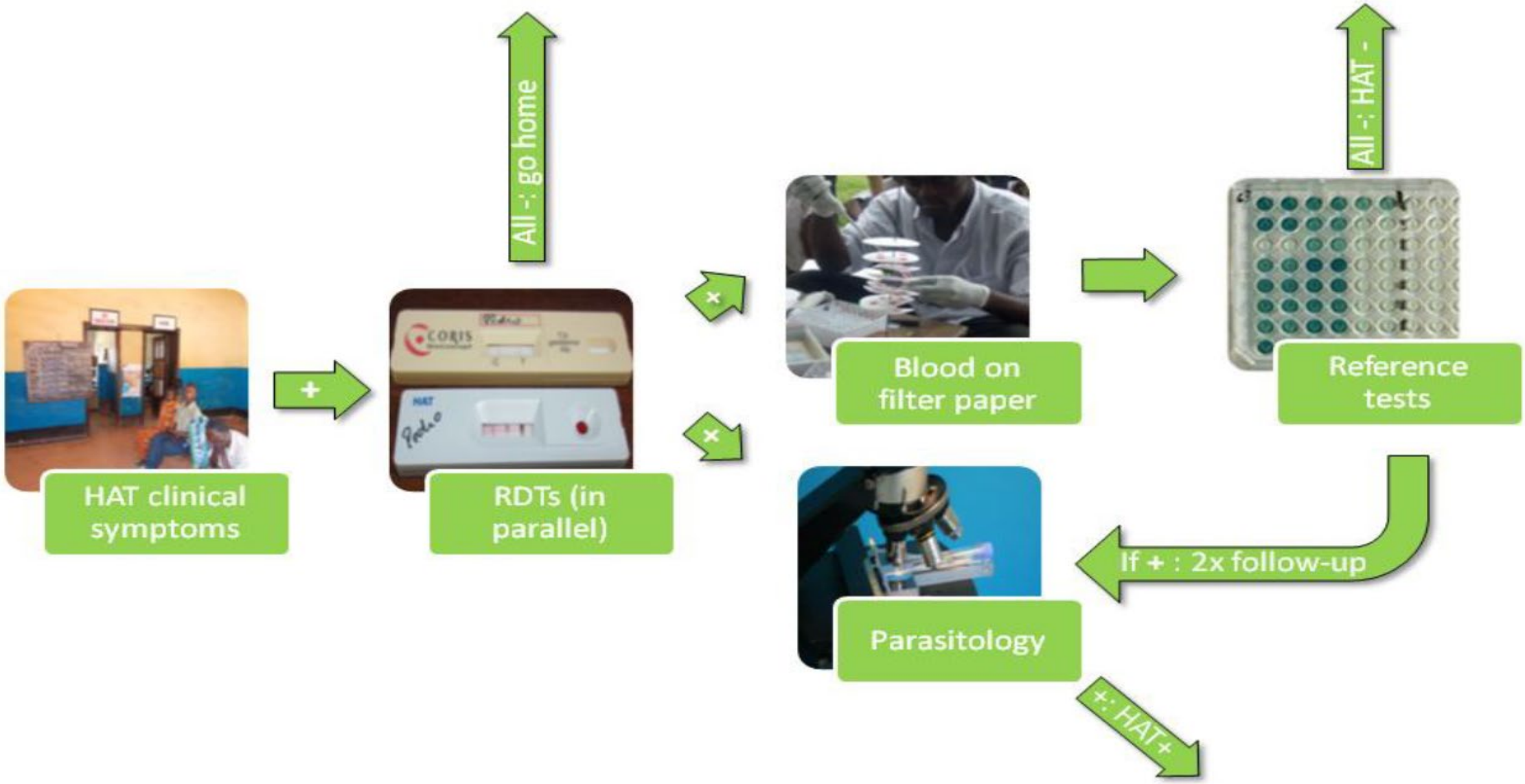
Methodology: Procedures

- Inclusions started in October 2017
- Clinical suspects are tested with HAT-Sero-*K*-Set, SD Bioline HAT, rHAT Serostrip
- Participants with at least 1 RDT +ve result will undergo, at CDT :
  - Parasitological examination (lymph node fluid examination, mAECT …);
  - Collection of blood on FP for reference tests (trypanolysis, LAMP, ELISA and real-time PCR)
  - Data-entry in a Personal Digital Assistant (PDA)



- RDT(s) +ve & Microscopy Trypano -ve subjects with 1 RT positive : microscopy parasitological testing at 3 and 6 months
- RDT(s) +ve & microscopy Trypano -ve subjects with all RT negative = considered as free of HAT
- For this presentation: Preliminary analyses based on PDA records only, inclusions until August 2018

Methodology: Procedures (2)



Results: enrolled participants characteristics

- 572 participants underwent RDT screening
- Excluded:
  - 18 participants no clinical sign suspecting HAT or missing clinical information
  - 9 participants with missing RDT results
  - 10 RDT+ participants with missing parasitological data
- 535 clinical HAT suspects enrolled (53.6% female, median age 26, IQR 17-42)
  - 15 referred from SSS to CDT
  - Persistent fever or headache reported respectively by 75% and 76% participants, both present for 63 % of participants.
  - Weight loss or weakness were positive for 31% and 29% of participants
  - Neurological signs were present for 28%

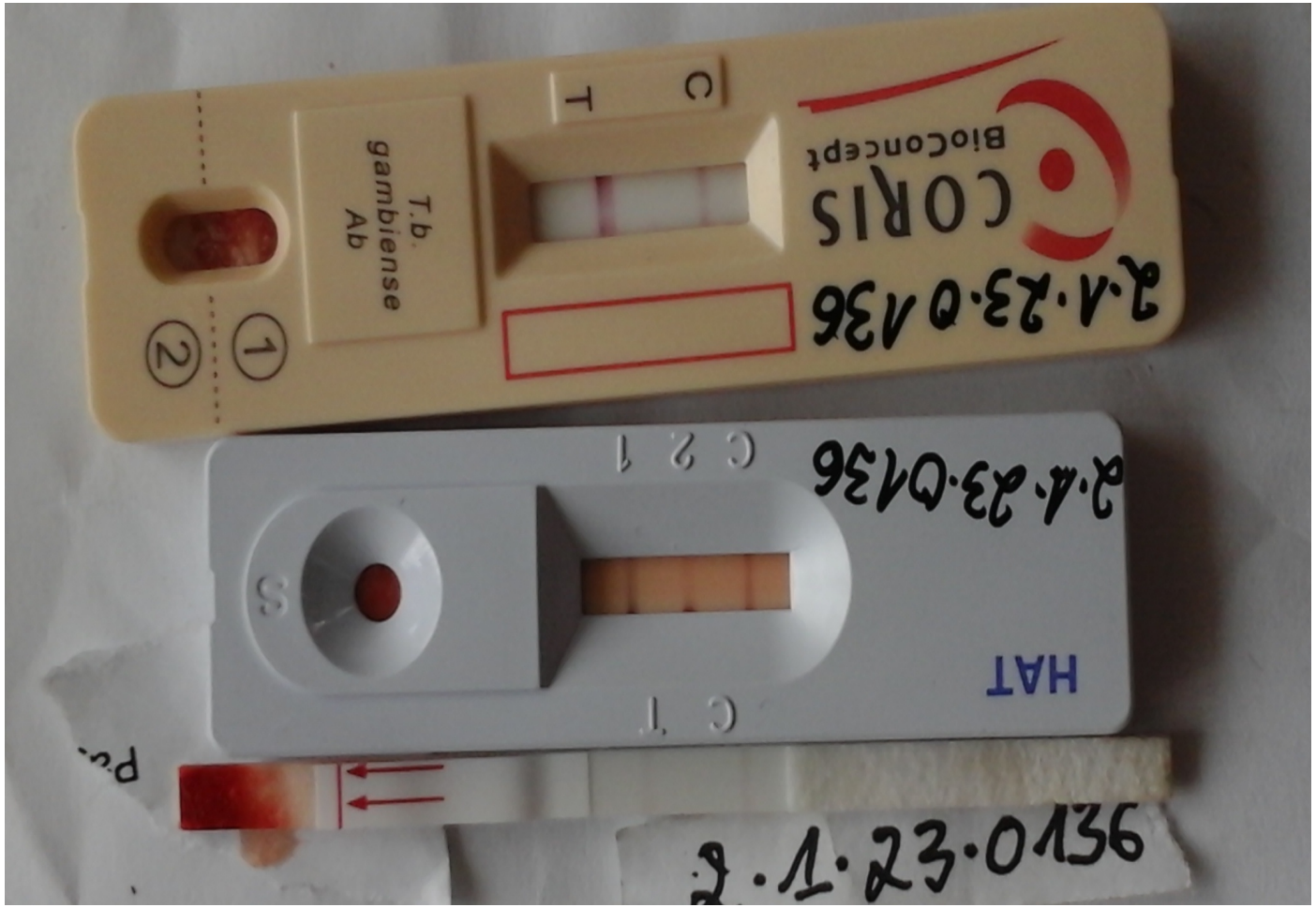
Results: Lab tests

- RDT results:
  - 427 (79.8%) participants negative in all RDTs (2 parasitology negative, 425 without parasitology results)
  - 108 (20.2%) positive in at least 1 RDT (RDT+)
- Parasitological results on RDT positives (at inclusion):
  - 25 confirmed HAT cases
  - 83 participants RDT(s) +ve but parasitology negative
- Reference Test (RT) results
  - 73 persons tested in RT out of 108 RDT+ (67.6%)
  - 39 RT positives out of 73 RT done
    - 19/25 confirmed HAT cases tested in RT, 19/19 RT positive
    - Among 20 RT+ and RDT+, only 6 /20 underwent 2nd parasitological examination and 1 of them 3rd parasitological examination: 1 additional HAT case confirmed at 3 months and 1 at 6 months, bringing total number of detected HAT cases to 27.

Results : Pictures for quality control

Camera on a microscope

Positive RDTs



Video of positive trypanosome sample at microscope

- 2_1_23_0136_1MA_20180715_121352.mp4

Sensitivity RDTs

- **"N"** = 27
  - **25** HAT cases at inclusion step
  - **+ 2** additional HAT cases at 3 and 6 months among positive RT participants
- **"n"** at **6 months**, with RT results input:
  - ✓**27**+ve to HAT Sero-*K*-set,
  - ✓**16** +ve to rHAT Sero Strip
  - ✓**24** +ve to SD Bioline HAT 1.0 RDT
  - ✓**27** +ve to HAT Sero-*K*-set or rHAT Sero Strip, **27** +ve to HAT Sero-*K*-set or SD Bioline HAT 1.0, **26** +ve to rHAT Sero Strip or SD Bioline HAT 1.0, **27** +ve to at least one out of 3 RDTs

Test	Sensitivity (95% CI)
HAT Sero-*K*-set RDT	100% (87.2 – 100)
SD Bioline HAT 1.0 RDT	92.3% (74.9 – 99.1)
rHAT Sero Strip RDT	59.3% (38.8 – 77.6)
rHAT Sero Strip or SD Bioline HAT 1.0 RDTs	96.3% (81.0 – 99.9)

Specificity

- **"N"** (RDT negative (no parasitological confirmation or negative) plus RDT +ve (which remained parasitological negative)
  - **508** HAT controls at 6 months (2 with SD Bioline HAT 1.0 DT and rHAT Sero Strip RDTs not performed)
- **"n"**
  - ✓**438** -ve to HAT Sero-*K*-set RDT, **494** -ve to rHAT Sero Strip RDT, **464** -ve to SD Bioline HAT 1.0 RDT, **435** -ve to both HAT Sero-*K*-set & rHAT Sero Strip RDTs, **398** -ve to both HAT Sero-*K*-set & SD Bioline HAT 1.0 RDTs, **427** -ve to both rHAT Sero Strip & SD Bioline HAT 1.0 RDTs, **397** -ve to both 3 RDTs

Test	Specificity (95% CI)
rHAT Sero Strip RDT	97.6% (95.9 – 98.8)
SD Bioline HAT 1.0 RDT	91.5% (88.7 – 93.8)
HAT Sero-*K*-set RDT	86.2% (82.9 – 89.1)
rHAT Sero Strip & SD Bioline HAT 1.0 RDTs	89.7% (86.6 – 92.3

Discussions (1)

- Strengths
  - 3 RDTs in parallel. Probably very few HAT cases missed.
  - Photos of all RDT positives and videos of parasitology positives
  - Additional parasitological analysis on RT positives useful: allows confirmation of additional HAT cases
- Limitations
  - Low reference rates to CDT (15 referred from SSS to CDT in at least 9 months, as 1-2 suspects referred and received by a CDT): to be improved!
  - Low number of 2nd and 3rd parasitological investigation on RDT and RT positives: to be increased. As a result: specificity probably underestimated
  - SD Bioline HAT 2.0: foreseen but still not available

Discussions (2)

- Test performance
  - Sero-*K*-Set RT is the most sensitive, so far no statistical difference compared to SD Bioline 1.0 RDT
  - rHAT SeroS RDT is the most specific (difference statistical significant)

- Preliminary results only:
  - Inclusions will continue for at least 12 months
  - Only results registered in PDA so far. Many SSS RDT negatives still missing from the analysis and specificity calculations
  - Cost data will be included in final analyses

Training: enrolment simulation

- DiTECT-HAT is part of the EDCTP2 programme supported by the European Union (DRIA-2014-306-DiTECT-HAT)