Validity of dried blood spot testing for sexually transmitted and blood-borne infections: A systematic review

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Background

- Testing for HIV and hepatitis C (HCV) using dried blood spot (DBS) specimens has been used in Canada for integrated bio-behavioural surveillance for almost two decades[1]

- DBS specimens are increasingly being used for screening and diagnostic purposes. Advantages of DBS over venipuncture include:
  - Collection is simple, less invasive and inexpensive
  - Less blood volume is required
  - Once dry, specimens are stable at room temperature for extended periods of time (~2 weeks)
  - Reduced risk of occupational exposures

- A large body of evidence supports the validity of older HIV-1 testing methodologies (i.e. 1st and 2nd generation EIAs) with DBS specimens however, an update is required regarding the validity of new testing methodologies for HIV-1 and other sexually transmitted and blood borne infections (STBBI)[2]

- A systematic review is being conducted to compile and assess the evidence regarding the validity of STBBI testing on DBS specimens

- Here we present our systematic review protocol and some preliminary findings

Source: https://www.cbc.ca/news/canada/prince-edward-island/pei-dry-blood-spot-testing-1.5024372

[1]Public Health Agency of Canada. Summary of key findings from I-Track phase 3 (2010-2012).
[2]Lim, M.D. Dried blood spots for global health diagnostics and surveillance: Opportunities and challenges. *American Journal of Tropical Medicine and Hygiene* **99,** 256-265 (2018)

Methods

1. **Research question**
   - What is the validity of STBBI testing on DBS versus standard biological specimens in populations aged 15 years and over measured in terms of sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), limit of quantification (LOQ), and/or limit of detection (LOD)?

2. **STBBIs of interest**
   - HIV-1, HIV-2
   - Hepatitis virus A, B, and C (HAV, HBV, HCV)
   - Herpes simplex virus (HSV-1, HSV-2)
   - Human T-cell lymphotropic virus (HTLV-1, HTLV-2)
   - Human papilloma virus (HPV)
   - *Chlamydia trachomatis* (chlamydia)
   - *Neisseria gonorrhoeae* (gonorrhea)
   - *Treponema pallidum* (syphilis)

3. **Information sources**
   - Peer-reviewed original research
   - Review articles
   - Systematic reviews
   - Meta-analyses
   - Health technology assessments
   - Randomized trials
   - Non-randomized trials
   - Key grey literature websites
   - Reference lists of all relevant peer-reviewed and grey literature
   - Internal documents from relevant organizations

4. **Search strategy**
   - Peer-reviewed and conducted under the guidance of a librarian
   - Utilized controlled vocabulary (e.g. MeSH headings) and keywords
   - Documents identified by searching EMBASE, Ovid MEDLINE, Elsevier Scopus, and key websites (ex: Canadian AIDS Treatment Information Exchange, CATIE)
   - Limited to human populations and documents in English or French

5. **Eligibility criteria**
   - ***Population:*** DBS specimens collected from any patient population 15 years of age or older regardless of socio-demographic characteristics and setting
   - ***Intervention:*** commercially available or "in-house" tests used to detect STBBIs from DBS specimens

5. **Eligibility criteria (continued)**
   - ***Comparison:*** commercially available or "in-house" tests used to detect STBBIs from "gold-standard" biological specimens
   - ***Outcome:*** measures of a validity including sensitivity, specificity, PPV, NPV, LOQ and/or LOD[3]
   - ***Exclusion criteria:*** (1) pathogen not of interest, (2) measures of validity not reported, (3) biological specimens other than blood, (4) DBS used to measure adherence to PrEP or ART, (5) participants <15 years of age, (6) intervention out of scope (i.e. blood dried on a matrix other than filter paper), (8) not original research, (9) documents in a language other than English or French
   - ***Assessment:*** Studies were independently assessed by two reviewers, and disagreements were resolved by third party consultation

6. **Data collection and analysis**
   - Information relevant to the outcomes and descriptive data recorded using a standardized table by a single reviewer
   - A second reviewer verified 20% of the data extraction for accuracy
   - Data extracted from selected studies was examined through a narrative synthesis approach[4] given the anticipated heterogeneity in terms of context, patient populations, and interventions

7. **Quality or risk of bias assessment**
   - Each document was assessed for quality and risk of bias using the QUADAS-2 tool[5], which was developed to assess the quality of primary diagnostic accuracy studies
   - Consists of four key domains: patient selection, index tests, reference standards, and flow and timing
   - Adjusted to this review's specific requirements by adding and/or omitting signaling questions:
     1. Patient selection: Did the study avoid the use of simulated patient samples?
        - Simulated patient samples were defined as DBS specimens prepared from pathogen negative whole blood spiked with laboratory-grown or commercially available analytes.
        - DBS specimens prepared from whole blood collected from patients in vacutainers versus direct finger pokes were also considered simulated patient samples.
     2. Index test: Did the study adhere to reasonable DBS storage conditions?
        - Reasonable DBS storage conditions were defined based on recommendations from the World Health Organization (www.who.int/hiv/topics/drugresistance/dbs_protocol.pdf). DBS can be stored up to 14 days at room temperature from the date of collection. Beyond 14 days, DBS should be store at -20˚C or colder.
   - Quality assessment (20%) was peer reviewed for accuracy

[3]Tibbetts, R.J. Verification and validation of tests used in the clinical microbiology laboratory. *Clinical Microbiology Newsletter* **33**, 153-160 (2015)
[4]Whiting, P.F. *et al.* QUADAS-2: A revised tool for the quality assessment of diagnostic Accuracy studies. *Annals of Internal Medicine* **155,** 529-536 (2011)
[5]Mays, N. *et al.* Systematically reviewing qualitative and quantitative evidence to inform management and policy-making in the health field. *Journal of Health Services and Policy* **10**, 6-20 (2005)

Results

Fig 1. Flow diagram of the systematic review modified from the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[5]

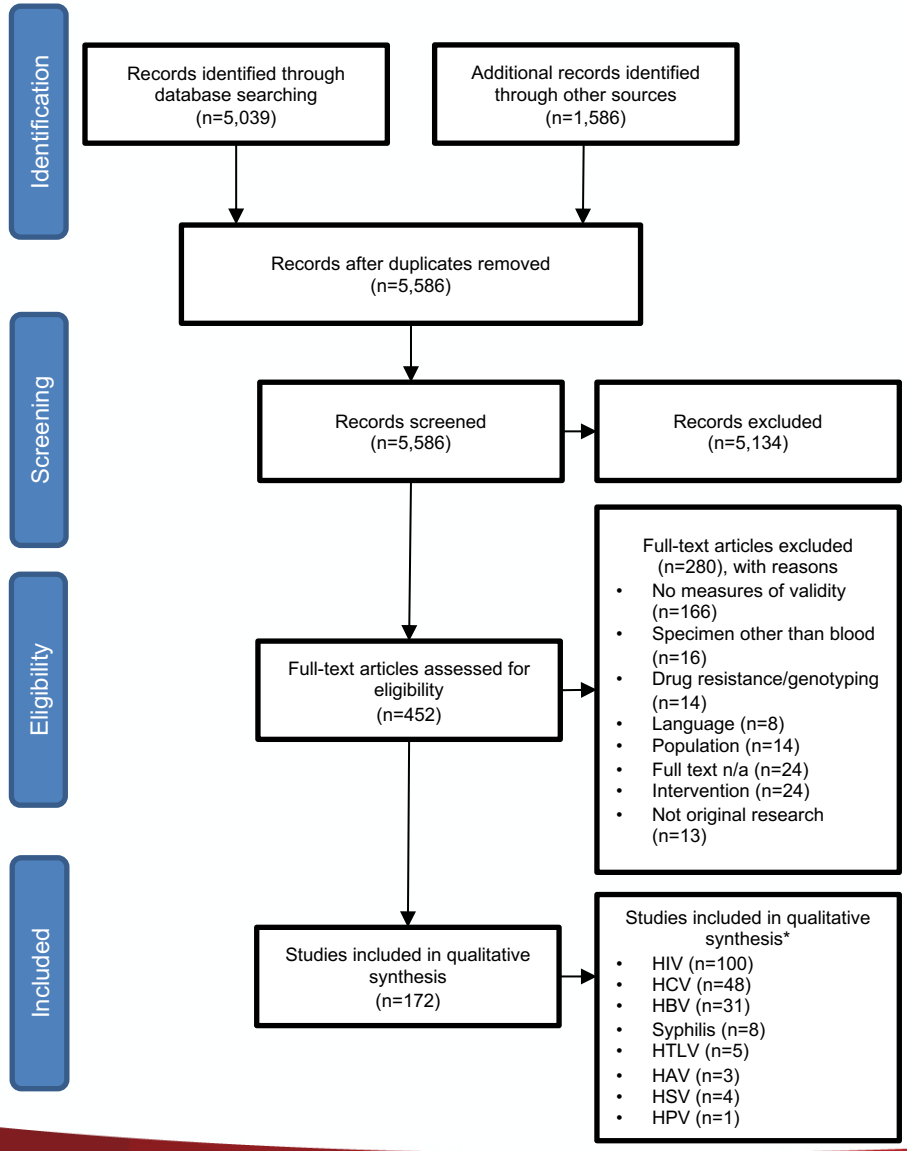
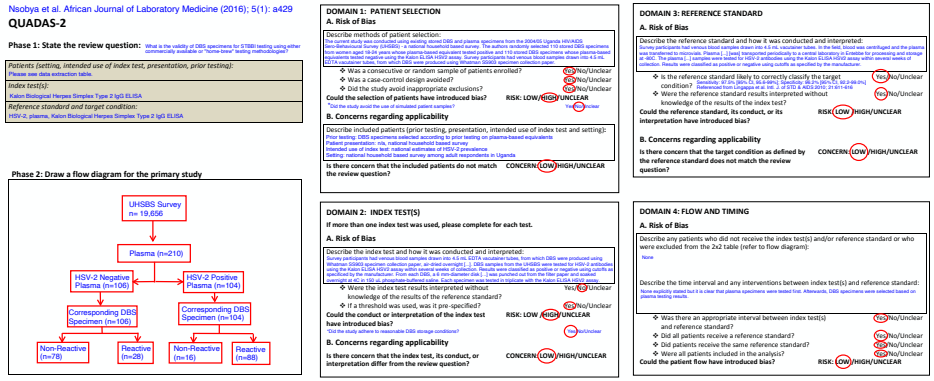


Fig 2. Sample data extraction relevant to the outcomes and descriptive data using a standardized table. Data found in the table are for illustrative purposes only.

Study	STBBI	Patient population	Patient sampling	Sample size (n=)	Index test	Se (%)	Sp (%)	PPV* (%)	NPV* (%)
Melgaço, *et al.* (2011)	HAV	University students (≥18 years of age)	Convenience	74 (8 positive + 66 negative)	Bioelisa HAV-EIA (Biokit)	100	100	100	100
Villar, *et al.* (2011)	HBV	Not reported	Convenience	142 (67 positive + 75 negative)	ETI-MAK-4 (Diasorin)	93	99	98	97
Brandão, *et al.* (2013)	HCV	HCV positive adults	Not reported	386 (40 positive + 346 negative)	Murex HCV AgAb (Abbott)	98	96	74	100
Garciá-Cisneros, *et al.* (2018)	HSV-2	Household survey (15-49 years of age)	Convenience	908 (166 positive, 162 negative, 602 indeterminate)	ELISA IgG-G2 HUMAN (Human Diagnostics)	90	87	85	92
Smit, *et al.* (2013)	Syphilis	Household survey	Convenience	463 (96 positive + 367 negative)	TPPA (Fujirebio)	85	99	NR	NR
Louie, *et al.* (2018)	HPV	University students (≥18 years of age)	Convenience, vaccination status	153 (50 positive + 103 negative)	In-house ELISA	94	98	96	97
Preux, *et al.* (1998)	HTLV	HTLV positive adults	Convenience, serostatus	109 (32 positive + 77 negative)	HTLV-1/2 ELISA (Abbott) + Bioptim 2.3 WB(Diagnostic Biotechnology)	81	100	NR	NR
Kania, *et al.* (2013)	HIV	HIV positive adults	Cluster, serostatus	218 (19 positive + 199 negative)	Genscreen ULTRA HIV Ag-Ab (Bio-Rad) + Inno-Lia HIV I/II Score (Innogenetics)	100	100	100	100

*PPV/NPV values only apply to populations tested with the proportion positive as indicated in the sample size column
Acronyms: Not reported (NR), Sensitivity (Se), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV)

Fig 3. Sample quality and risk of bias assessment using the QUADAS-2 tool. Data from Nsobya, SL., *et al.* Performance of Kalon herpes simplex virus 2 assay using dried blood spots among young women in Uganda. *AJLM* **5**(1): 429. doi: 10.4102/ajlm.v5i1.429 are being used for illustrative purposes below.



[5]Moher, D., *et al.* Preferred reporting items for systematic reviews and meta-analyses: The Prisma statement. *PLoS Medicine* **6**, e1000097 (2009)
*Some studies reported on more than one STBBI

Results (continued)

Fig 4. Index tests reported for HCV testing on DBS specimens. Data found in this figure are for illustrative purposes only and represent a subset (n=35/48) of all studies reporting HCV testing on DBS specimens included for data extraction and analysis.

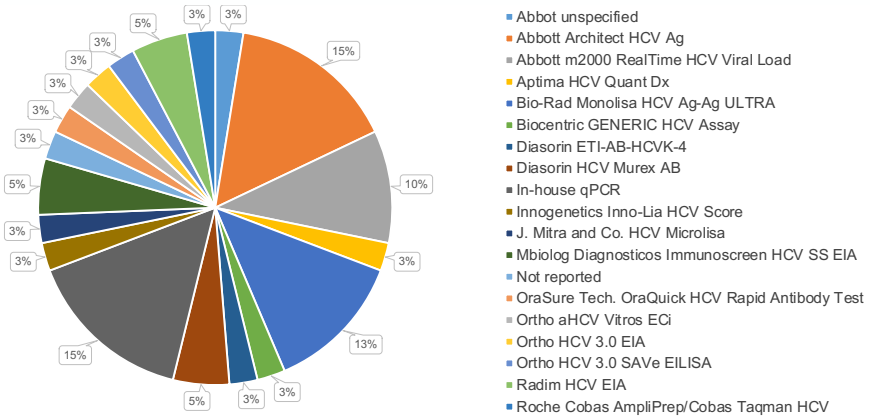
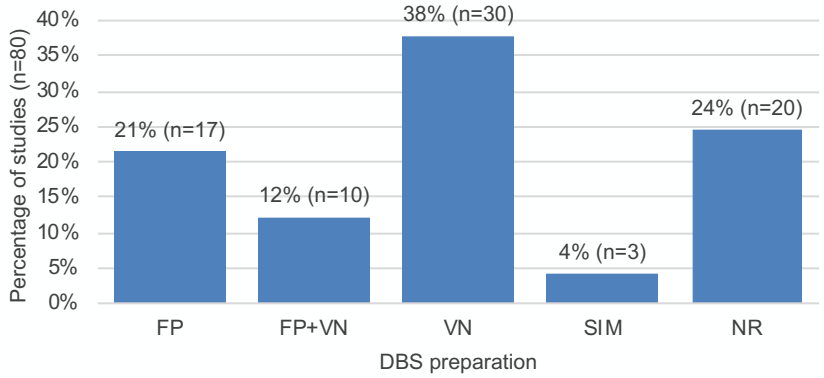


Fig 5. Collection methods reported for DBS specimen preparation. Data found in this figure are for illustrative purposes only and represent a subset (n=80/172) of all studies reporting STBBI testing on DBS specimens included for data extraction and analysis. The use of venipuncture and/or simulated patient samples could result in significant bias since whole blood is typically collected in vacutainers containing anti-coagulants (e.g. EDA, heparin) which have been shown to impact testing accuracy.



*Finger poke, FP; finger poke and venipuncture, FP+VN; venipuncture, VN; simulated patient samples, SIM; not reported, NR.

Conclusion

- Most of the literature regarding STBBI testing on DBS is for HIV and hepatitis C
- Preliminary analysis of findings support the validity of DBS testing for certain STBBI where sufficient evidence was available
  - Potential for significant bias due to patient sampling and experimental conditions
- Direct comparison (e.g. meta-analysis) will be challenging
  - Wide variety of commercial kits and experimental conditions reported
  - Overall, poor reporting of relevant experimental conditions
- Guidelines that describe all relevant experimental conditions and assay characteristics are needed for reporting STBBI testing on DBS specimens
- We anticipate to complete the systematic review by summer 2020