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Short communication

Demonstration of the diagnostic agreement of capillary and venous blood samples, using hepatitis-C virus SD Bioline© rapid test: A clinic-based study

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ABSTRACT

Background: Simplifying hepatitis C virus (HCV) screening is a key step in achieving the elimination of HCV as a global public health threat by 2030.

Objectives: The objective of this study was to demonstrate the agreement of capillary blood and venipuncture specimens when using SD Bioline© HCV, a low-cost rapid diagnostic test (RDT), prequalified by WHO in 2016 on venous blood samples.

Study design: Recruitment was conducted prospectively among adult patients presenting for HCV testing at the Médecins Sans Frontières (MSF) clinic of Preah Kossamak Hospital (Phnom Penh, Cambodia) between October and November 2017. Capillary and venous blood samples were collected from consenting patients and tested with SD Bioline© HCV. Two independent, blinded readers, and in the case of disagreement, a third reader, interpreted the results of each blood sample. Concordance between results was compared using Cohen's Kappa interrater reliability statistic. Discrepant sample pairs were tested with an enzyme immunoassay, the reference standard, at the Institute Pasteur of Cambodia.

Results: Among 421 pairs of samples collected, reader disagreement occurred for 0.7% (n = 3) of the participants. Sixty-four percent of capillary and venous blood sample pairs tested positive for HCV, with a Kappa statistic of 0.985 between the two methods. Three participants with discrepant sample pair results tested positive with EIA.

Conclusions: Capillary and venous blood samples were concordant when tested with HCV SD Bioline© in a clinical context. This simplified testing approach is essential to the scale-up of HCV screening and useful in resource-limited settings or among populations for whom venipuncture is problematic.

1. Background

With the introduction of efficacious treatments for hepatitis C virus (HCV), the target set by the World Health Organization (WHO) for the elimination of HCV as a global public health threat by 2030 may be envisioned [1]. However, among the estimated 71 million people currently infected with HCV worldwide, only approximately one in five have been diagnosed. This proportion is estimated to be as low as 8% in resource-limited countries, which bear over two-thirds of the disease burden [1].

The scale-up of simplified approaches to screening is the gateway to HCV treatment [2]. HCV screening generally involves the detection of anti-HCV antibodies using whole blood with enzyme immunoassays (EIAs) [3]. Rapid diagnostic tests (RDTs) offer simplicity and rapidity, require few testing materials, and can be performed by lay personnel with minimal training. RDTs could be used without confirmatory testing when they meet analytical standards and are quality-assured [4].

In 2016, the in vitro immunochromatographic RDT SD Bioline© HCV (Standard Diagnostics, Inc., Rest of World regulatory version,

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manufactured in the Republic of Korea), which has high sensitivity (99.3%) and specificity (98.1%), was prequalified by the WHO for the qualitative detection of HCV antibodies in human serum, plasma, and venous whole blood [5]. At the time of the study, capillary blood collected by finger-prick was not included in the manufacturer's evaluation, and subsequent WHO pre-qualification, as a specimen type for SD Bioline© HCV testing. However, there is strong evidence that capillary blood can yield high quality results, correlating to traditional venipuncture reference values.

2. Objectives

The present study aimed to assess the agreement of capillary and venous whole blood samples with the SD Bioline© HCV test in a clinical context.

3. Study design

The study was conducted in Cambodia, a lower-middle income country where viral hepatitis is a major public health issue. HCV seroprevalence is estimated to range between 0.87% and 14.7% [6].

This cross-sectional, prospective evaluation was conducted at Médecins Sans Frontières (MSF) HCV clinic at the Preah Kossamak national hospital in Phnom Penh, Cambodia. All patients aged 18 years and older and coming for HCV testing between October 9th and November 10th, 2017, were invited to participate. Those previously diagnosed with HCV were excluded.

The National Ethical Committee for Health Research (NECHR) and the Ministry of Health of Cambodia approved the present study. All participants provided written informed consent. After consenting, participants underwent testing for HCV by trained laboratory staff with the SD Bioline© HCV test as per the manufacturer's instructions [5] using two different 10 µl specimens, assessed simultaneously: 1) Venous whole blood drawn in a 2 mL ethylenediaminetetra-acetic acid BD Vacutainer tube, and 2) Capillary blood obtained from finger-prick, using a 10 µL pipette (Capillary tube 10 µl Blue line©, AIMBIO Inc, Republic of Korea) to transfer blood onto the testing device. After 20 min, test results were read separately by two blinded, independent readers. When a control line was apparent and readers agreed, samples were labelled as either "positive" if a reactive line was apparent, or "negative" if it was absent. In the case of disagreement, a third blinded reader acted as a tie-breaker. Readers were asked to report if the reactive line was weak. Patients were informed of the venous blood test result.

When the results of the venous and capillary sample pairs were discrepant, a second venous blood sample of 4 mL was collected and sent on the same day to the Institute Pasteur of Cambodia for confirmation using Eclysis® Anti HCV II (Roche Diagnostics GmbH), an EIA.

Lastly, the four laboratory technicians and 11 nurses employed by the study were asked about their blood sampling method preferences.

Anonymized demographic information and the tests results were collected on a standardized form. Data were double entered into a Research Electronic Data Capture database (REDCap, version 13) [7] and analyzed using Stata©, version 13 (College Station, Texas, USA).

4. Results

4.1. Demographics

A total of 421 out of 423 eligible patients were included, among whom 63.7% (n = 268) were women. The median age was 54 years ([IQR]: 45–61).

4.2. Reader agreement

Overall, 63.9% (n = 269) of the capillary blood samples and 64.1% (n = 270) of the venous whole blood samples were interpreted as positive. Disagreement between the readers concerned 0.7% (n = 3) of participants, for both their capillary and venous blood samples. All instances of reader disagreement involved weak reactive lines: one reader saw a weak reactive line while the other interpreted the result as non-reactive.

Overall, weak reactive lines occurred for 10.7% of positive venous and 11.1% of positive capillary specimens, and concerned 30 participants.

Table 1
Comparison of SD Bioline HCV results of capillary versus venous blood samples (N = 421).

Capillary blood	Venous blood	Positive	Negative	Total
	Positive	268	1	269
	Negative	2	150	152
	Total	270	151	421

4.3. HCV seroprevalence and sample agreement

Overall, 63.7% (n = 268) of the capillary and venous whole blood sample pairs were interpreted as positive (Table 1). Among the 421 sample pairs, reader disagreement occurred for three samples—with weak reactive lines.

The percent agreement was 99.3% (n = 418/421) and the kappa statistic was 0.985 (95%CI: 0.967–1.000). All three patients with discrepant sample pair results were HCV positive using an EIA. These three discrepant sample pairs were not necessarily the ones concerned by reader disagreement.

4.4. Staff feedback

The majority of the 15 laboratory technicians and nurses stated that they preferred capillary blood sampling. They felt that testing was "faster", "safer" in terms of infection control, and "simpler", as no specialized skills were required. All mentioned that they believed patients also favored the capillary blood sampling method.

For all samples, venous and capillary, the main concern was the weak reactive lines, which were challenging to read.

5. Discussion

This study demonstrates the agreement of capillary blood samples and venous blood samples using SD Bioline© HCV in an urban hospital, with excellent kappa agreement. Our findings are in line with the manufacturer's recent assessment, in a laboratory setting, of the performance of capillary blood samples, added to the WHO prequalification of SD Bioline© HCV in January 2018 [5].

Furthermore, our results show a marked preference by study staff for the finger-prick sampling method.

A concerning issue is the non-negligible proportion (≈11%) of weak reactive lines, making the interpretation of test results challenging; nevertheless disagreement between readers was rare. The similar proportions of weak lines for capillary and full blood samples and the quality control procedures in place suggest that the weak lines were associated with the test itself, or characteristics specific to some patients, rather than the testing process. Hence, large-scale use of SD Bioline© HCV must take this issue into account, first in the form of comprehensive training on the interpretation of results, and secondly by ensuring proper conditions for the testing process (such as proper lighting).

A limitation of this study is that the capillary blood specimens tested were not assessed against the EIA reference due to operational constraints. However, since SD Bioline© HCV venous blood testing was

found by the WHO to have 100% specificity and sensitivity against the WHO EIA standard [5], its use was appropriate for evaluating the diagnostic concordance of paired specimens.

Finally, in this study, trained laboratory technicians performed the tests, which may limit the generalizability of our findings. Additional studies may promote testing conducted by non-specialized staff.

When testing with RDTs, capillary blood sampling for HCV is adapted to large-scale screening. It can be used outside traditional clinical settings, to offer testing to vulnerable or marginalized populations, such as people who inject drugs for whom intravenous access is difficult. Lastly, the finger-prick method has been shown in other contexts to be more readily accepted by patients [8].

Accordingly, we recommend the systematic evaluation of the diagnostic agreement of capillary blood sampling when developing new screening tools.

In the context of global under-diagnosis of HCV, this study advances the simplification of HCV screening by demonstrating, in a clinic, the agreement of capillary and venous blood samples using the WHO-prequalified SD Bioline© HCV test; this finding has the potential to reduce barriers to timely diagnosis.

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Conflict of interest

All co-authors declare that they have no conflict of interests.

CRediT authorship contribution statement

Chhorvy Sun: Data curation, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Momoko Iwamoto:** Data curation, Formal analysis, Methodology, Supervision, Validation, Writing - original draft, Writing - review & editing. **Aurelie Calzia:** Investigation, Resources, Validation, Writing - review & editing. **Bun Sreng:** Investigation, Resources, Writing - review & editing. **Sokchea Yann:** Resources, Visualization, Writing - review & editing. **Sorphorn Pin:** Resources, Writing - review & editing. **Celine Lastrucci:** Conceptualization, Methodology, Writing - review & editing. **San Kimchamroeun:** Resources, Writing - review & editing. **Chhit Dimanche:** Methodology, Resources, Writing - review & editing. **Jean-Philippe Dousset:** Project administration, Supervision, Writing - review & editing. **Mickael Le Paih:** Funding acquisition, Writing - review & editing. **Suna Balkan:** Funding acquisition, Visualization, Writing - review & editing. **Tonia Marquardt:** Funding acquisition, Project administration, Writing - review & editing. **Valentina Carnimeo:** Methodology, Writing - review & editing. **Pascale Lissouba:** Writing - original draft, Writing - review & editing. **David Maman:** Conceptualization, Funding acquisition, Methodology, Writing - review & editing. **Anne Loarec:** Conceptualization, Methodology, Supervision, Validation, Writing - review & editing.

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