How do we diagnose the undiagnosed: a challenge for simplification

Mario Poljak

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Faculty of Medicine, University of Ljubljana, Slovenia
Global continuum of care for HCV infection and 2030 WHO elimination targets
MAKE THE PROCESS SIMPLE
THEN MAKE IT SIMPLER
AND THEN GO BACK AND MAKE EVEN MORE SIMPLE.

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All patients with suspected HCV infection should be tested for anti-HCV antibodies in serum or plasma as first-line diagnostic test (A1).

Screening for HCV infection should be based on the detection of anti-HCV antibodies in serum or plasma by means of enzyme immunoassay (A1).

EASL. J Hepatol 2018;69:461-511

An anti-HCV test is recommended for HCV testing ... (I,A).
Automated immunoassay analysers

- highly standardised
- reliable
- quick
- random access
- for low-, mid-, high-volume demand
Integrated immunoassay and clinical chemistry analyzers

Siemens

Abbott

Roche

Ortho / Johnson&Johnson

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MAKE IT SIMPLER!
HCV screening: anti-HCV point-of-care testing?

Rapid diagnostic tests (RDTs) using serum, plasma, fingerstick whole blood or crevicular fluid (saliva) as matrices can be used instead of classical enzyme immunoassays at the patient’s care site to facilitate anti-HCV antibody screening and improve access to care (A2).

EASL. J Hepatol 2018;69:461-511
Point-of-care anti-HCV tests

should follow the ASSURED criteria for the ideal rapid test (WHO)...

A = Affordable
S = Sensitive
S = Specific
U = User-friendly (simple to perform in a few steps with minimal training)
R = Robust and rapid (results available in less than 30 minutes)
E = Equipment-free
D = Deliverable to those who need the test

30 different tests evaluated

substantial heterogeneity between studies

performances varied widely among individual point-of-care tests

overall pooled sensitivity 97.4% (95% CI: 95.9-98.4)

overall pooled specificity 99.5% (99.2-99.7)

OraQuick had the highest test sensitivity and specificity and showed better performance than a third generation enzyme immunoassay in seroconversion panels
Development of a SERS-Based Rapid Vertical Flow Assay for Point-of-Care Diagnostics

O. J. R. Clarke,† B. L. Goodall,‡ H. P. Hui,‡ N. Vats,‡ and C. L. Brosseau*†

†Department of Chemistry, Saint Mary’s University, Halifax, Nova Scotia Canada, B3H 3C3
‡MedMira Laboratories Inc., Halifax, Nova Scotia, Canada, B3S 1B3

Supporting Information

ABSTRACT: Point-of-care (POC) diagnostic testing platforms are a growing sector of the healthcare industry as they offer the advantages of rapid provision of results, ease of use, reduced cost, and the ability to link patients to care. While many POC tests are based on chromatographic flow assay technology, this technology suffers from a lack of sensitivity along with limited capacity for multiplexing and quantitative analysis. Several recent reports have begun to investigate the feasibility of coupling chromatographic flow platforms to more advanced read-out technologies which in turn enable on-site acquisition, storage, and transmission of important healthcare metrics. One such technology being explored is surface-enhanced Raman spectroscopy or SERS. In this work, SERS is coupled for the first time to a rapid vertical flow (RVF) immunotechnology for detection of anti-HCV antibodies in an effort to extend the capabilities of this commercially available diagnostic platform. High-quality and reproducible SERS spectra were obtained using reporter-modified gold nanoparticles (AuNPs). Serial dilution studies indicate that the coupling of SERS with RVF technology shows enormous potential for next-generation POC diagnostics.
Analytical performance of newly developed rapid point-of-care test for the simultaneous detection of hepatitis A, B, and C viruses in serum samples


Oh Joo Kweon MD, Yong Kwan Lim MD, Hye Ryoun Kim MD, Tae-Hyoung Kim MD, Mi-Kyung Lee MD

- EuDx HE(A, B, C) Kit
  - HAV IgM
  - HBsAg
  - HCV IgG
- Control line (C)
- Test line (T)
- Sample/buffer well

Positive patterns:
- HAV IgM (+)
- HBsAg (+)
- HCV IgG (+)
- Negative

Invalid patterns:
- HAV HBV HCV
- HAV HBV HCV
- HAV HBV HCV
- HAV HBV HCV
Separation of Plasma from Whole Blood by Use of the cobas Plasma Separation Card: a Compelling Alternative to Dried Blood Spots for Quantification of HIV-1 Viral Load

Sergio Carmona, Britta Seiverth, Dieketseng Magubane, Lucia Hans, Matthias Hoppler
Early phase of HCV infection

Transfusion settings

High-risk groups (IVDU, hemodialysis patients, HIV positive individuals, organ donors)
HCV screening: anti-HCV + HCV RNA?

In the case of:
- suspected acute hepatitis C,
- in immunocompromised patients,
- in patients on haemodialysis,
HCV RNA testing in serum or plasma should be part of the initial evaluation (A1).

EASL. J Hepatol 2018;69:461-511
Short communication

Twenty-four mini-pool HCV RNA screening outside a blood transfusion setting: Results of a 2-year prospective study

Katja Seme a, Tina Močilnik a, Kristina Fujs a, Dunja Z. Babič a, Aleksandra Todorović b, Tamara Fras-Stefan b, Mario Poljak a, *

Short communication

Twenty-four mini-pool HCV RNA screening in a routine clinical virology laboratory setting: A six-year prospective study

Katja Seme, Tina Močilnik, Mario Poljak *
24 mini-pool HCV RNA screening routine diagnostic laboratory setting

86,309 anti-HCV negative specimens (4,060 mini-pools) tested by HCV RNA 24 mini-pool screening strategy between 1 June 2004 and 31 May 2019

100 (1 : 863) anti-HCV negative/HCV RNA positive samples detected

57 anti-HCV negative/HCV RNA positive patients detected

anti-HCV-negative, PCR-positive blood donors Slovenia, 2008-2017 = 1 : 924,087
HCV screening: after anti-HCV positivity?

If anti-HCV antibodies are detected, the presence of HCV RNA, or alternatively HCV core antigen (if HCV RNA assays are not available and/or not affordable) in serum or plasma should be determined to identify patients with ongoing infection (A1).

Reflex testing for HCV RNA in patients found to be anti-HCV antibody-positive should be applied to increase linkage to care (B1).

If anti-HCV antibodies are detected, HCV RNA should be determined by a sensitive molecular method with a lower limit of detection ≤15 IU/ml (A1).
HCV RNA!
Half a Diagnosis: Gap in Confirming Infection among Hepatitis C Antibody-positive Patients

Emily McGibbon, MPH, Katherine Bornschlegel, MPH, Sharon Balter, MD
New York City Department of Health and Mental Hygiene, Long Island City, NY.

ABSTRACT

BACKGROUND: Recent guidelines recommend testing all individuals born during 1945-1965 for hepatitis C virus (HCV) antibody. For antibody-positive patients, subsequent RNA testing is necessary to determine current infection status. This study aimed to assess whether clinicians order HCV RNA tests as recommended for antibody-positive patients and to identify barriers to such testing.

METHODS: We sampled individuals newly reported to the New York City Department of Health and Mental Hygiene’s HCV surveillance system and collected information from clinicians. For patients without RNA test results, we asked the reason an RNA test was not ordered and requested that the clinician order the test.

RESULTS: Of 245 antibody-positive patients, 67% were tested for HCV RNA (for 21% of these, the test was ordered only after our request); 33% had no RNA testing despite our request. Patients without RNA testing were seen in medical facilities (47%), detox facilities (30%), and jail/prison (15%). Reasons RNA testing was not done were that the patient did not return for follow-up (35%), the facility does not do RNA testing (22%), and the patient was tested in jail (15%).

CONCLUSIONS: In our study, one third of patients did not get complete testing for accurate diagnosis of HCV, which is essential for medical management. Additional education for clinicians about the importance of RNA testing may help. However, with improved antiviral treatments now available for HCV, it is time for reflex HCV RNA testing for positive antibody tests to become routine, just as reflex Western blot testing is standard for human immunodeficiency virus.

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Molecular diagnostic systems 1.0
Molecular diagnostic systems 2.0+
- fully automated sample-to-result fashion
- multiple tests performed concordantly
- sample number flexibility
- STAT test prioritization
- random access?
MAKE IT SIMPLER!
Rapid/point-of-care HCV RNA tests?
The desire is to have self-contained, fully integrated sample-to-report devices that accept raw, untreated specimens, perform all of the molecular steps, and provide interpreted test results in < 1 h.
Selected compact “sample in-results out” molecular diagnostic devices

Cepheid GeneXpert
Roche cobas Liat System
Alere iSystem
Luminex ARIES
Atlas Genetics
Enigma Diagnostics
Micronics
Cirrus Dx T-COR 8
BioFire FilmArray
Nanosphere Verigene SP
QuantuMDx
Janssen Diagnostics
Rheonix Encompass Optimum
GenMark Dx eSensor
Veredus VereChip
Great Basin Portrait
Focus Dx Simplexa/3M Cycler
Quidel Savanna & Solana
Meridian Illumigene
BD Max System
ELITE InGenius Systems
Biomeme
Fluorescentric Inc.
GeneWEAVE VivoDx
Evaluation of the Xpert HCV Viral Load point-of-care assay from venepuncture-collected and finger-stick capillary whole-blood samples: a cohort study

Jason Grebely, Francois M J Lamoury, Behzad Hajarizadeh, Yasmin Mowat, Alison D Marshall, Sahar Bajis, Philippa Marks, Janaki Amin, Julie Smith, Michael Edwards, Carla Gorton, Nadine Ezard, David Persing, Marika Kleman, Philip Cunningham, Beth Catlett, Gregory J Dore, Tanya L Applegate, on behalf of the LiverLife Study Group

Lancet Gastroenterol Hepatol 2017;2:514-520

Background Point-of-care hepatitis C virus (HCV) RNA testing offers an advantage over antibody testing (which only indicates previous exposure), enabling diagnosis of active infection in a single visit. In this study, we evaluated the performance of the Xpert HCV Viral Load assay with venepuncture and finger-stick capillary whole-blood samples.

Methods Plasma and finger-stick capillary whole-blood samples were collected from participants in an observational cohort enrolled at five sites in Australia (three drug and alcohol clinics, one homelessness service, and one needle and syringe programme). We compared the sensitivity and specificity of the Xpert HCV Viral Load test for HCV RNA detection by venepuncture and finger-stick collection with the Abbott RealTime HCV Viral Load assay (gold standard).

Findings Of 210 participants enrolled between Feb 8, 2016, and July 27, 2016, 150 participants had viral load testing results for the three assays tested. HCV RNA was detected in 45 (30% [95% CI 23–38]) of 150 participants based on Abbott RealTime. Sensitivity of the Xpert HCV Viral Load assay for HCV RNA detection in plasma collected by venepuncture was 100·0% (95% CI 92·0–100·0) and specificity was 99·1% (95% CI 94·9–100·0). Sensitivity of the Xpert HCV Viral Load assay for HCV RNA detection in samples collected by finger-stick was 95·5% (95% CI 84·5–99·4) and specificity was 98·1% (95% CI 93·4–99·8). No adverse events caused by the index test or the reference standard were observed.

Implications The Xpert HCV Viral Load test can detect active infection from a finger-stick sample, which represents an advance over antibody-based tests that only indicate past or previous exposure.
fully portable PCR instrument based on asymmetric PCR and detection by a secondary hybridisation probe and dissociation curve analysis

not „sample-to-answer” (plasma preparation), no RNA extraction step

dimensions 12x18x10 cm; weight 600 g


European study:
sensitivity 98.6%, specificity 100%
invalid results: 26/925 (2.8%)
invalid results after retesting: n=10

Real-life study in Africa:
sensitivity 100%, specificity 100%
invalid results: 6/130 (4.6%)
invalid results after retesting: n=4
Evaluation of a routine point-of-care intervention for early infant diagnosis of HIV: an observational study in eight African countries

Flavia Bianchi*, Jennifer Cohn*, Emma Sacks, Rebecca Bailey, Jean-Francois Lemaire, Rhoderick Machekano, on behalf of the EGPAF POC EID Study Team†

POC testing in 339 health-care facilities:
- 2,875 infants exposed to HIV tested with conventional testing methods
- 18,220 infants tested with POC testing

the return of results to caregivers within 30 days: **18.7% vs. 98.3%**

the median time from sample collection to return of results: **55 days vs. 0 days**

the median time from sample collection to ART initiation: **49 days vs. 0 days**

infants with HIV initiating antiretroviral therapy within 60 days: **43.3% vs. 92.3%**

the cost per test result returned within 30 days: **$131 vs. $27**
In low- and middle-income countries, and in specific settings in high-income countries, a qualitative HCV RNA assay with a lower limit of detection ≤1,000 IU/ml (3.0 log10 IU/ml) can be used to provide broad affordable access to HCV diagnosis and care (B2).

Anti-HCV antibody screening for HCV infection can be replaced by a point-of-care HCV RNA assay with a lower limit of detection ≤1,000 IU/ml (3.0 Log10 IU/ml) or HCV core antigen testing, if such assays are available and the screening strategy proves to be cost-effective (C2).
Lab-on-a-USB key

microfluidic devices integrated with USB key data storage devices

a device attached to other computational devices such as a cell phone or laptop computer to control molecular assays being done on the microfluidic biochip

analysis transmitted to central databases for shared use and meta-processing
Novel pH sensing semiconductor for point-of-care detection of HIV-1 viremia

R. Gurrala¹, Z. Lang², L. Shepherd², D. Davidson², E. Harrison², M. McClure¹, S. Kaye¹, C. Toumazou²,³ & G. S. Cooke⁴

The timely detection of viremia in HIV-infected patients receiving antiviral treatment is key to ensuring effective therapy and preventing the emergence of drug resistance. In high HIV burden settings, the cost and complexity of diagnostics limit their availability. We have developed a novel complementary metal-oxide semiconductor (CMOS) chip based, pH-mediated, point-of-care HIV-1 viral load monitoring assay that simultaneously amplifies and detects HIV-1 RNA. A novel low-buffer HIV-1 pH-LAMP (loop-mediated isothermal amplification) assay was optimised and incorporated into a pH sensitive CMOS chip. Screening of 991 clinical samples (164 on the chip) yielded a sensitivity of 95% (in vitro) and 88.8% (on-chip) at >1000 RNA copies/reaction across a broad spectrum of HIV-1 viral clades. Median time to detection was 20.8 minutes in samples with >1000 copies RNA. The sensitivity, specificity and reproducibility are close to that required to produce a point-of-care device which would be of benefit in resource poor regions, and could be performed on an USB stick or similar low power device.
A smartphone dongle as point-of-care device
Loop-mediated isothermal amplification (LAMP)
Ustar Biotechnologies (Hangzhou, China)
Cross Priming Amplification technology developed by Qimin You, while conducting research in Canada & US

- instrument free specimen processing
- isothermal nucleic acid amplification
- visual read-out detection and easy data interpretation
- cross contamination prevention
- reagents stable at ambient temperature
Paper-based microfluidics for DNA diagnostics of malaria in low resource underserved rural communities

Julien Reboud\textsuperscript{a,1}, Gaolian Xu\textsuperscript{b,1}, Alice Garrett\textsuperscript{a}, Moses Adriko\textsuperscript{c}, Zhugen Yang\textsuperscript{a}, Edridah M. Tukahebwa\textsuperscript{c}, Candia Rowell\textsuperscript{c}, and Jonathan M. Cooper\textsuperscript{a,2}

PNAS 2019; 116:4834-4842
Handheld isothermal amplification and electrochemical detection of DNA in resource-limited settings

Maria-Nefeli Tsaloglou\textsuperscript{a,c}, Alex Nemiroski\textsuperscript{a}, Gulden Camci-Unal\textsuperscript{a}, Dionysios C. Christodoulou\textsuperscript{a}, Lara P. Murray\textsuperscript{a}, John T. Connelly\textsuperscript{c}, George M. Whitesides\textsuperscript{a,b,*}

\textit{Anal Biochem} 2018;543:116-21

the first fully integrated, POC device that combines isothermal DNA amplification with electrochemical detection on paper
rapid (<30 min) and sensitive (<10 copies) visual detection of amplified products using pH-sensitive dyes with minimal buffering capacity achieved with loop-mediated isothermal amplification (LAMP)

**specificity**

**sensitivity**
non-instrumented nucleic acid amplification, single-used disposable (NINA-SUD) devices for the detection of HIV-1 in whole blood using reverse-transcription, loop-mediated isothermal amplification (RT-LAMP) with lyophilized reagents

NINA-SUD heating device harnesses the heat from an exothermic chemical reaction initiated by the addition of saline to magnesium iron powder

lyophilized HIV-1 RT-LAMP reagents stable at 30°C for up to one month
HCV core antigen in serum or plasma is a marker of HCV replication that can be used instead of HCV RNA to diagnose acute or chronic HCV infection when HCV RNA assays are not available and/or not affordable (A1).

Anti-HCV antibody screening for HCV infection can be replaced by a point-of-care HCV RNA assay with a lower limit of detection ≤1,000 IU/ml (3.0 Log10 IU/ml) or HCV core antigen testing, if such assays are available and the screening strategy proves to be cost-effective (C2).

EASL. J Hepatol 2018;69:461-511
HCV core antigen
back to the future?
Review

The role of core antigen detection in management of hepatitis C: a critical review☆

Katja Semea, Mario Poljaka,*, Dunja Z. Babiča, Tina Močilnika, Adriana Vinceb

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Received 6 October 2004; accepted 12 October 2004

Abstract

Several assays in research format and two commercial assays for the detection of hepatitis C virus (HCV) core protein or HCV core antigen have been developed in recent years. In order to elucidate the role and significance of HCV core antigen detection in the diagnosis and management of hepatitis C, we reviewed 56 studies published in peer-reviewed journals until September 2004. Evaluations in transfusion settings showed that the HCV core antigen assay detects HCV infection, similarly as nucleic acid techniques (NAT), between 40 and 50 days earlier than the current third generation HCV antibody screening assays. HCV core antigen levels closely track HCV RNA dynamics, and allow clinical monitoring of a patient’s therapy, independently of HCV genotype, however, mainly in the samples with HCV RNA levels above 20,000 IU/ml. Considering the lower sensitivity of HCV core antigen detection in comparison to NAT, the HCV core antigen assay is not practical for the determination of the end of treatment response and sustained viral response, but could be useful for the determination of early viral response in the pegylated interferon-alpha and ribavirin treated patients infected with HCV genotype 1. The HCV core antigen detection is a viable tool for study of hepatitis C pathogenesis. The HCV core antigen can be used as a marker of HCV replication in anti-HCV positive individuals in the areas of the world that cannot afford NAT and/or in the settings that are not equipped or competent to perform HCV RNA testing. Because the manufacturer of HCV core antigen assays recently stopped an active marketing of these assays in several countries, it will, unfortunately and probably, never be possible to determine the actual potential and usefulness of HCV core antigen testing in the management of hepatitis C.

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HCV Core Ag vs. HCV RNA - CORRELATION

Cut off: 2.5 pg/ml

$r=0.81; p<0.001$
SLO - Patient 5

![Graph showing HCV RNA and HCV Core Ag concentrations over time.](Image)

- HCV RNA
- HCV Core Ag

Time (months): 0, 3, 8, 12, 18, 27, 34, 40, 43, 47, 50, 53, 59, 63, 65

HCV RNA concentrations: 1e5, 3e5, 5e5, 7e5, 9e5

HCV Core Ag concentrations: 0, 40, 80, 120, 160

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HCV core antigen assays

ARCHITECT HCV Ag assay (Abbott Diagnostics)

Ortho HCV cAg enzyme immunoassay (Ortho Clinical Diagnostic)

HCV Ag ELISA (Hunan Jynda Bioengineering Group)

Lumipulse Ortho HCV Ag (Fujirebio)

Lumispot HCV Ag assay (Eiken)
HCV core antigen as an alternative to HCV RNA testing in the era of direct-acting antivirals: retrospective screening and diagnostic cohort studies

Lancet Gastroenterol Hepatol 2018;3:856-64


retrospective screening cohort study in Ontario, Canada

75/80 HCV RNA positive samples positive for HCV core antigen
- sensitivity 94% (95% CI 86-98)

0/993 HCV RNA negative samples tested positive for HCV core antigen
- specificity 100% (95% CI 94-100)

HCV core antigen testing can be used instead of HCV RNA testing for diagnosis and documentation of treatment adherence; inferior for SVR determination

lower costs, improved access to care, particularly in low- and middle-income countries
HCV proteins expressed in all six major HCV genotypes

simultaneously detects HCV-Ags through a standard EIA platform

HCV-Ags EIA detects all four HCV proteins in serum specimens

lowest limit of detection equivalent to serum HCV RNA levels of 150-250 IU/mL
An improved gold nanoparticle probe-based assay for HCV core antigen ultrasensitive detection

Hui-qiong Yin\textsuperscript{a}, Chang-fu Ji\textsuperscript{a,1}, Xi-qin Yang\textsuperscript{b}, Rui Wang\textsuperscript{a}, Shu Yang\textsuperscript{a}, He-qiu Zhang\textsuperscript{b}, Jin-gang Zhang\textsuperscript{a,\ast}

\textsuperscript{a} Beijing Institute of Transfusion Medicine, Beijing 100850, China
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A B S T R A C T

A gold nanoparticle probe-based assay (GNPA) was developed for ultrasensitive detection of Hepatitis C virus (HCV) core antigen. In the GNPA, after anti-HCV core antigen polyclonal antibodies and single-stranded barcode signal DNA were labeled on gold nanoparticle probe (NP), DNA enzyme was used to degrade the unbound barcode DNAs. The anti-HCV core antigen monoclonal antibodies were coated on magnetic microparticles probe (MMP). Then the NP-HCV core antigen-MMP sandwich immuno-complex was formed when the target antigen protein was added and captured. Magnetically separated, the immuno-complex containing the single-stranded barcode signal DNA was characterized by TaqMan probe based real-time fluorescence PCR. A detection limit of 1 fg/ml was determined for the HCV core antigen which is magnitude greater than that of ELISA (2 ng/ml). The coefficients of variation (CV) of intra-assay and inter-assay respectively ranged from 0.22–2.62\% and 1.92–3.01\%. The improved GNPA decreased the interference of unbound barcode DNAs and may be an new way for HCV core antigen detection.

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No RIBA/INNO-LIA necessary anymore!

false positive anti-HCV screening test vs. naturally resolved hepatitis C
MAKE IT SIMPLER!
Geenius HCV Supplemental Assay (BioRad)

unitary disposable test based on lateral flow immuno-chromatography and using a strip in a cassette

duration of the testing: 20 min

anti-HCV antibodies against NS3, NS4, NS5 and capsid antigens

3 sample types (serum, plasma, whole blood)

expert interpretation software; full traceability
Whole blood sampled on dried blood spots can be used as an alternative to serum or plasma obtained by venipuncture for anti-HCV antibody testing, after shipment to a central laboratory where the enzyme immunoassay will be performed (A2).

Whole blood sampled on dried blood spots can be used as an alternative to serum or plasma obtained by venipuncture for HCV RNA testing, after shipment to a central laboratory where the molecular test will be performed (A2).

EASL. J Hepatol 2018;69:461-511
Dried Blood Spots: A Tool to Ensure Broad Access to Hepatitis C Screening, Diagnosis, and Treatment Monitoring

Table 2. Performance of Anti–Hepatitis C Virus (HCV) Antibody Detection, HCV Core Antigen Detection, HCV RNA Detection, and HCV Genotype Determination on Whole-Blood Specimens Collected With the Dried Blood Spot Technique

<table>
<thead>
<tr>
<th>Variable</th>
<th>Specificity, % (95% CI)</th>
<th>Sensitivity, % (95% CI)</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-HCV antibody detection</td>
<td>98.2 (94.9–99.6)</td>
<td>99.1 (97.4–99.8)</td>
<td>99.1</td>
<td>98.2</td>
</tr>
<tr>
<td>HCV core antigen detection</td>
<td>100 (97.8–100)</td>
<td>64.1 (58.5–69.3)</td>
<td>100</td>
<td>64.7</td>
</tr>
<tr>
<td>HCV RNA detection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CAP/CTM</td>
<td>100 (97.8–100)</td>
<td>97.1 (94.7–98.5)</td>
<td>100</td>
<td>95.0</td>
</tr>
<tr>
<td>m2000</td>
<td>100 (97.8–100)</td>
<td>98.1 (95.9–99.1)</td>
<td>100</td>
<td>96.6</td>
</tr>
<tr>
<td>HCV genotype determination</td>
<td>NA</td>
<td>72.3 (67.0–76.9)</td>
<td>100</td>
<td>NA</td>
</tr>
</tbody>
</table>

Results of serum analysis are the references.

Abbreviations: CAP/CTM: Cobas Ampliprep/Cobas TaqMan HCV assay, version 2; CI, confidence interval; m2000, m2000 platform; NA, not applicable; NPV, negative predictive value; PPV, positive predictive value.
delivery of samples or standard POC instruments and reagents by drones

Poljak M, Šterbenc A.
Use of drones in clinical microbiology and infectious diseases: current status, challenges and barriers.
Clin Microbiol Infect 2020; in press.
Rwanda is the first country that has sought to integrate drones into its health service with drones used to deliver blood; launched in 2016

4,100 units of blood delivered in the first year; delivery time 15-45 minutes; 40% of the blood for postpartum hemorrhaging; 40% for treatment of severe malaria

Tanzania launched the world’s largest drone delivery network in January 2018

more than 1,000 health facilities across the Tanzania connected
delivery of blood, vaccines and malaria and HIV/AIDS drugs
modified Zipline International drones flying at 100 km (62 miles) per hour; drones parachuting blood and medicines with biodegradable parachutes
Sample transport

clin micro lab
three paired samples obtained from 56 adult volunteers; chemistry, hematology, and coagulation testing

168 samples held stationary vs. 168 samples flown in the UAS (6-38 minutes)

33 of the most common chemistry, hematology, and coagulation tests performed

a mean difference of 3.2% for glucose and <1% for other analytes

only bicarbonate did not meet the strictest performance criteria.

transportation of laboratory specimens via small UASs does not affect accuracy of routine chemistry, hematology, and coagulation tests results
Drone Transport of Chemistry and Hematology Samples Over Long Distances

Timothy K. Amukele, MD, PhD, James Hernandez, MD, Christine LH. Snozek, PhD, Ryan G. Wyatt, FPC, Matthew Douglas, MD, Richard Amini, MD, and Jeff Street

Drones take laboratory logistics to a new level

A Swiss hospital group is using drones to fly medical laboratory specimens between its key centres, Mark Nicholls reports.

In what is believed to be a world first, the eight-hospital Ticino EOC organisation has partnered with Swiss Post and US drone manufacturer Matternet to spearhead faster, more efficient specimens transport. The trial is being held for flights covering the 1.3 km between two of its Lugano hospitals, the Ospedale Civico and Ospedale Italiano.

While each hospital has its own emergency room and laboratory, the laboratory at Ospedale Italiano, in the city centre, closes at 5pm and at weekends. Presently the blood samples are transported between the two hospitals by local taxis, explained hospital director Luca Jelmoli. This is, of course, subject to the availability and to traffic conditions. Therefore, to ensure transport that’s always available and economically more interesting, we decided to apply the new technologies and use drones to transport our blood samples in those time slots when one of the laboratories is closed.

There are already clear benefits from using drones in this way; the transport time does not depend on traffic conditions or third parties, cost is lower than by taxi, and the drone can fly over hills and mountains, considerably reducing the length of transportation compared to the road.

At the moment, when snow makes road driving more difficult, drones will still operate and avoid delays in delivering specimens and test results. Whilst the distance between the hospitals is relatively small, Jelmoli told European Hospital that the drone can actually fly as far as 20 km, which means Ticino EOC is already considering a future possibility of transporting laboratory samples from other hospitals even further away.

The first phase of the initiative involved proving the technical feasibility and acquiring official licenses and permits for the autonomous flights over populated areas, and this has been completed. With the approval of the Federal Office for Civil Aviation (FOCA), the trial will now move to the second phase later this year, which will see drone transport integrated into the hospital processes.

‘That will be to test the integration of drone transport with the emergency room and laboratory processes,’ Jelmoli explained. ‘This will be supported by a specific device, being developed by the supplier, which will autonomously load and unload the drone and charge the batteries.

Phase three will see day-to-day usage of drones to transport blood samples between the hospitals, with hospital staff launching the drone via a smartphone application. The drone will then fly autonomously along the predefined route to its destination, where another staff member will receive the box.

Some observers have raised concerns that the acceleration and movement of drones might affect the quality and integrity of blood samples but, in a separate study conducted at John Hopkins University in Baltimore, researchers have shown this is not the case.

The Matternet logistics drone used in Lugano is a quadcopter, 80 cm in diameter (without rotor blades). Able to carry up to 2 kg and with a top speed of 56 km/h, the drone can operate in temperatures of -10 to +40°C and at an altitude of 50-100 m above the ground.

Safety features include a parachute in case of total drone failure, but all the drones’ on-board critical components are replicated in case of malfunction.

However, the test phase has seen more than 80 flights without any problems and the hospital believes transportation with drones will be as secure as transportation with a taxi. Once the drone meets all the strict requirements regarding safety, practicality and reliability, they will be in daily use between the two Ticino EOC hospitals – some time in 2018.

Luca Jelmoli became CEO of the two public 300+ bed hospitals in Lugano, Switzerland (Ospedale regionale di Lugano) in 2012. He graduated from the ETH Zurich (Swiss Federal Institute of Technology) in 1992 and gained his MBA from Kellogg University in Chicago, USA. Initially he worked in the pharmaceutical industry, then in retail, business development and corporate finance. In 2007 he became CEO of a leading Swiss clinic specialised in reproductive medicine.
Sample transport and rent-a-POC concept

POC = point-of-care

POC storage, maintenance, calibration and QC

clin micro lab
Optimizing a Drone Network to Deliver Automated External Defibrillators

Circulation 2017;135:2454-65

successful in-flight PCR amplification using convective thermocycling of two different DNA targets (16 min in-flight reaction time)
Lab-on-a-drone

time-resolved fluorescence detection and quantification using a smartphone camera and integrated image analysis app
Lab-on-a-drone

Drone-based centrifugation

Benchtop centrifugation processes are challenging to miniaturize by removing the quadcopter propellers and replacing them with 3D printed centrifuge rotors designed to fit the motor shaft threading.

Drone-based sample preparation

Standard centrifuge-based workflows allowed in lab-on-a-drone, 3D printed attachments transform the quadcopter into a centrifuge capable of rotation speeds up to 10,000 rpm.

Standard column-based extraction of Dengue viral RNA from human serum yielded results on par with those obtained from samples processed using a benchtop centrifuge.
Hepatitis C - WHO prequalified IVDs (September 2019)

Bioelisa HCV 4.0
Murex anti-HCV 4.0
INNOTEST HCV Ab IV

OraQuick HCV Rapid Antibody Test Kit
InTec Rapid Anti-HCV Test
SD BIOLINE HCV

INNO-LIA HCV Score

ARCHITECT HCV Ag assay

Xpert HCV Viral Load Test
Eliminating hepatitis C

WHO has ambitious global targets, made feasible by new highly effective treatments. But drugs alone are not enough. Talha Burki reports.

Egypt almost finished the process of testing its entire adult population, and to treat 2.5–3 million people within 6 months of diagnosis.

Egypt cut the cost of each anti-HCV antibody test to around $0.50.

Millions Flock to Free Tests as Egypt Seeks to Eradicate Hepatitis C

By Mahmoud Mourad and Lena Masri
December 06, 2018
Number of anti-HCV tests conducted and positive test results among persons who inject drugs — Georgian Harm Reduction Network, Georgia, 2006-2018
Louisiana will pay up to $58 million USD annually or up to $290 million USD for access to the generic form of sofosbuvir/velpatasvir (Epclusa).

$58 million = same amount of money the state spent in the current budget year for hep C treatments for prisoners and Medicaid patients.

unlimited access to the medication started on 15 July 2019.
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