Hepatitis C Screening Guideline Development Group
Background to recommendation 24: What is the role of rapid diagnostic tests and point of care tests in HCV screening?

The purpose of this document is to provide the background information to the formulation of recommendations by the Guideline Development group.

Not all evidence in this document is presented in the National Clinical Guideline.

The National Clinical Guideline is available from: http://health.gov.ie/national-patient-safetyoffice/ncec/national-clinical-guidelines/

Contents

History of development of the recommendation

Date	Process	Outcome
02/06/2015	Recommendations from quality appraised national and international guidelines reviewed	Agreed that review of literature required
19/01/2017	GDG subgroup meeting to undertake considered judgement process	Formulation of recommendation
23/02/2017	Review of subgroup recommendation by GDG	Recommendation accepted
25/04/2017	Consultation feedback reviewed by GDG	No changes to recommendation
June – July 2017	Editing	Recommendation reworded in final editing process

Considered judgement process

The considered judgment form completed by the GDG subgroup in formulating the recommendations is presented below. Please note the final wording of the recommendation may have changed after review of the GDG, after the consultation process, or during the editing process.

Date: 20 January 2017
Attendees: NOF, CDG, JC, ER, SD

Table 1: Considered judgement form

1. What is the question being addressed? Present PICO if relevant
How should screening be implemented for each group for which screening is recommended, including **what is the role for point-of-care testing (PoC) /rapid diagnostic testing (RDT)?**
2. What evidence is being considered to address this question and why? (This section will explain the approach taken to address this question and what GDG members are being asked to consider)
Guidelines and primary research literature are being considered in order to assess the technical performance of PoC/RDT and also the non-technical performance e.g. acceptability to patients and/or healthcare providers, impact on testing rates etc
3. What is the body of evidence? Source of evidence: (tick all that apply) ✓ Guidelines ✓ Primary literature Other □ ; specify: _____
Current Guidelines for PoC/RDT **WHO 2016** (1) Recommendations on which serological assays to use: • To test for exposure to hepatitis C infection in adults and children (> 18 months of age), an HCV serological assay (antibody or antibody/antigen) using either **RDT** or laboratory-based immunoassay formats that meet minimum safety, quality and performance standards (with regard to both analytical and clinical sensitivity and specificity) is recommended • In settings where there is limited access to laboratory infrastructure and testing and/or in populations where access to rapid testing would facilitate linkage to care and treatment, RDTs are recommended Strong recommendation, low/moderate quality of evidence due to serious risk of bias, inconsistency and imprecision in studies identified (WHO 2016 (draft report) Guidelines on hepatitis B and C testing) **CDC 2013** (2) Update of 2003 CDC Guidelines for laboratory testing and results reporting of antibody to hepatitis C virus due to the availability of the OraQuick HCV rapid antibody test. Testing for HCV begins with either a rapid or a laboratory conducted assay for HCV antibody in blood (CDC 2013 Testing for HCV infection: an update of guidance for clinicians and laboratories. HIQA quality score 121) **Literature Review – Technical performance**

Khurhoo et al 2015 (3) (updated a previous systematic review and meta-analysis published by Shivkumar et al in 2012)
Thirty studies that evaluated 30 tests fulfilled the inclusion criteria. Performances varied widely among individual PoC tests. The overall pooled sensitivity, specificity, positive likelihood-ratio, negative likelihood-ratio and diagnostic odds ratio for all tests were 97.4% (95% CI: 95.9–98.4), 99.5% (99.2–99.7), 80.17 (55.35–116.14), 0.03 (0.02–0.04), and 3032.85 (1595.86–5763.78), respectively. This suggested a high pooled accuracy for all studies. Substantial heterogeneity between studies was found, but none of the subgroups investigated could account for the heterogeneity. Of the seven tests evaluated in the meta-regression model, OraQuick had the highest test sensitivity and specificity and showed better performance than a third generation enzyme immunoassay in seroconversion panels. The next highest test sensitivities and specificities were from TriDot and SDBioline, followed by Genedia and Chembio. The Spot and Multiplo tests produced poor test sensitivities but high test specificities. Nine of the remaining 23 tests produced poor test sensitivities and specificities and/or showed poor performances in seroconversion panels, while 14 tests had high test performances with diagnostic odds ratios ranging from 590.70 to 28822.20.

Literature Review – Non-technical performance

Drobnik et al 2011(4) conducted a qualitative study in New York city of provider attitudes to rapid testing (OraQuick on oral fluid) through focus groups and a qualitative survey. Staff had a significantly more positive attitude to OraQuick rapid test compared to the standard blood test on the following criteria - explaining test procedure, administering test, integrating prevention messages and appropriateness of the test. The service providers were more likely to recommend the OraQuick test to clients. Focus group results that supported RDT were; no need for follow up appointments, 20 minute turnaround time for results allowed time for education and counselling, ability to focus attention then on those who test positive, ability to provide testing in more settings, reduced risk to staff, challenges that phlebotomy can cause for many clients, challenges accessing sufficiently skilled phlebotomists due to limited resources, and potential to incorporate rapid HCV testing in combination with rapid HIV testing. However focus groups also articulated that RDT could result in increased testing and the measures that would be required to address this. In addition there would be need for blood testing for some populations e.g. immigrant populations who require HBV screening. Limitations of this study were: study of provider attitudes to rapid testing as opposed to service users, response rate and number of responses were not reported, high risk study population (5 of the 6 clinics were for IDUs and 2 served immigrant populations).

Jewett et al 2013 (5) conducted a qualitative research study in an urban STD clinic and HIV testing facility in the USA on the use of the OraQuick test using venous blood samples from phlebotomy. Patients (n=12) and staff (n=19) were recruited. HCV negative (n=9) patients were pleased with the rapid test and the fact that they received their test results on the same day. Three of the nine HCV negative patients reported fear of the phlebotomy needle. For HCV positive patients (n=3) one said that the rapidity of the test made it easier and one patient said that because all tests were carried out at the same time it made it easier. Triage staff revealed the PoC test was quick, accurate and simple to use. Health care providers said that the fact that the PoC test gave the same day results could be used as a way to promote the test. Limitations of this study were the very small sample size. Authors provided limited information on how participants were recruited. Phlebotomy was used to collect the sample for PoC test. Focus groups were of short duration. Attitudes to the rapid test were only one outcome explored in this study.

Morano et al 2014 (6) carried out a cross sectional study in the USA. High risk patients attending a mobile clinic were offered a choice between PoC test (OraQuick) with fingerstick and standard

test with phlebotomy. The response rate was 32.6%. 47.7% of those tested chose PoC test and 52.3% chose the standard phlebotomy test. Those who selected PoC were more likely to be white, US born, have >15 lifetime sexual partners. IDU patients were less likely to choose the PoC test. Those choosing PoC were significantly more likely to be linked to care within 30 days. The study did not include collection of data on why patients selected the PoC or standard test. The study findings are potentially biased by the fact that the PoC test only tested for HCV whereas standard phlebotomy tested for HCV, HBV, HAV, HIV and Syphilis which were all free of charge to the patient. External validity of the study is influenced by the high risk population group and mobile clinic setting.

Hayes et al 2014 (7) in the USA recruited 129 participants who were initially offered either RDT (OraQuick) with finger prick or standard test with phlebotomy and 126 completed a survey specifically about preferences, perceptions and reasons for test choice.
→82.9% chose to receive the RDT test. The majority (60.2%) chose the RDT because they wanted fast results. Most (84.4%) who received the RDT agreed that they preferred receiving their results the same day. Very few participants (3.1%) agreed that it would have been better to wait a week to receive their results. 62.3% reported that the rapid test was just as or more accurate than the conventional phlebotomy test, and 53.5% reported that the finger-prick was less or much less painful. 97.5% agreed that they understood their results. The majority (93.9%) would recommend the rapid test to a friend.
→21 of 22 participants who opted for the standard HCV test completed the questionnaire. The most common reason given for choosing the standard (n = 8, 38.1%) was because they felt it was older and more trusted. Other participants stated that they did not want their results that day (n = 3, 14.3%), felt that the standard test was more convenient (n = 3, 14.3%), were afraid of fingers pricks (n = 2, 9.5%), or felt that the standard test was less painful (n = 1, 4.8%).
→The study findings are potentially biased by the fact that all clients had phlebotomy (for RNA) regardless of initial test choice and those who had the RDT were aware of their test result prior to completing the survey. The external validity of this study is limited by the high risk population (young IDU) that participated.

Coats and Dillon (8) carried out a systematic review of studies that contained quantitative data on the frequency of testing and/or new diagnoses after the introduction of PoC testing of high-risk populations. They did not find any studies that introduced PoC testing and determined its effect on frequency of testing or new diagnoses.

Cost effectiveness studies
Schackman et al (9) compared the cost effectiveness of no HCV testing referral or offer, off site HCV testing, on-site rapid HCV testing (with OraQuick), and onsite rapid HCV and HIV testing in a substance abuse treatment programme. They took a lifetime horizon and discounted costs and utilities at a rate of 3% per year. Compared to no testing, onsite rapid HCV testing had an incremental cost effectiveness ratio of $18,300 per quality adjusted life year (QALY) compared with no testing. Offsite referral was dominated by onsite rapid testing. Onsite rapid HCV and HIV testing had an ICER of $64500 compared to onsite rapid HCV testing alone. Results were similar when different treatment regimes, including an interferon free regime were considered**.**

4. What is the quality of the evidence? To be considered if primary literature was reviewed.

4.1. How reliable are the studies in the body of evidence?

If there is insufficient evidence to answer the key question go to section 11. Comment here on any issues concerning the quantity of evidence available on this topic and its methodological quality.

4.2. Are the studies consistent in their conclusions – comment on the degree of consistency within the available evidence. Highlight specific outcomes if appropriate. If there are conflicting results highlight how the group formed a judgement as to the overall direction of the evidence

The systematic review by Khuroo et al**Error! Bookmark not defined.** included studies on a number of different PoC/RDT tests and found that technical performance varied widely among individual tests studied.
The studies on non-technical performance of PoC/RDT varied in terms of populations studied (patients Vs providers), methods used, outcomes examined, and study findings. Most patient groups studied were high-risk.

4.3. Generalisability – are the patients in the studies similar to our target population for this guideline? is it reasonable to generalise

Technical: Only 5 of the 30 included studies in Khuroo's systematic review were from high endemnicity countries. The patient populations studied mainly represented hospital patients (various sources) and blood donors. 4 studies amongst specific high-risk populations were included.
Non-technical performance: All 4 studies were carried out in the USA. Three of the four studies were carried out among high risk populations e.g. IDUs. The fourth study offered testing to patients who had at least one risk factor for HCV infection.

4.4. Applicability - Is the evidence applicable to Ireland? Is the intervention/ action implementable in Ireland?

Yes

4.5. Are there concerns about publication bias? Comment here on concerns about all studies coming from the same research group, funded by industry etc

Technical performance: The systematic review by Khuroo et al**Error! Bookmark not defined.** contained 30 studies examining a number of different tests.
Non-technical performance: Assessing acceptability of a test requires qualitative methodology which is harder to carry out and may not be as readily published.

5. Additional information for consideration

5.1. Additional literature if applicable e.g. Irish literature

Nil

5.2. Relevant national policy

Nil

5.3. Epidemiology in Ireland if available and applicable

Nil

6. Potential impact of recommendation

6.1. Benefit versus harm

What factors influence the balance between benefit versus harm? Take into account the likelihood of doing harm or good. Do the desirable effects outweigh the undesirable effects?

PoC/RDT with finger-prick sampling could increase the accessibility of testing.
The provision of immediate results could immediately alleviate anxiety in those who test negative
There is some evidence that RDTs may improve linkage-to-care

PoC/RDT tests provide immediate HCV antibody results but do not enable additional testing. Therefore patients who are antibody positive will require further testing to establish HCV status. Further testing will require venepuncture and standard laboratory testing. Therefore PoC/RDT doesn't currently eliminate the need for venepuncture. In addition some RDTs require serum or plasma samples with centrifugation before testing.

6.2. What are the likely resource implications and how large are the resource requirements?

Consider cost effectiveness, financial, human and other resource implications

PoC/RDT with finger-prick sampling could increase the number of tests done and could improve linkage to care both of which would require an increase in resources. However, the ability to provide results immediately would reduce the resources required to follow-up all patients who would otherwise have to be recalled for their results. In addition RDT that use finger-prick blood do not require specially trained phlebotomists / clinicians. However those who test anti-HCV positive will require further testing using venous blood.

6.3. Acceptability – Is the intervention/ option acceptable to key stakeholders?

While the currently approved PoC/RDT available in Ireland (OraQuick) can use oral fluid, the sensitivity of oral fluid is low (see CJF on specimen type). The sensitivity is not considered acceptable to recommend this test using oral fluid.
Using OraQuick with finger prick blood can be awkward to perform and may not be as acceptable to the provider or patient.

6.4. Feasibility - Is the intervention/action implementable in the Irish context?

HCV PoC/RDT are not routinely used for screening or diagnosis in Ireland. They have only been used for research purposes.

Not all tests are fully approved

- OraQuick has been FDA approved – does not require venous blood. Oral fluid and finger-stick blood can be used
- SD Bioline HCV is WHO prequalified – requires venous blood

6.5. What would be the impact on health equity?

The use of RDT might enable an increase in testing amongst hard-to-reach populations with greater linkage to care. This would result in a positive impact on health equity.

7. What is the value judgement? How certain is the relative importance of the desirable and undesirable outcomes? Are the desirable effects larger relative to undesirable

As oral fluid is not considered an acceptable specimen type, only PoC/ RT using blood were considered. While RDT/ PoC tests may confer some benefit in preventing loss to follow up, as they only test for antibody at present, venepuncture will still be required to test for Ag or RNA to confirm infection.

8. Final Recommendations

√ Strong recommendation
□ Conditional/ weak recommendation

Text:

- Screening and diagnostic testing for HCV infection should be performed on serum or plasma
- Where concerns exist about hard-to-reach populations or linkage-to-care then consideration could be given to using approved (eg FDA / CE) rapid diagnostic tests on blood specimens
- If RDT/PoC tests are introduced into standard clinical practice then a quality assurance programme should be established that addresses internal quality control and external quality assurance.

9. Justification

While RDT/ PoC tests may confer some benefit in preventing loss to follow up, as they only test for antibody at present, venepuncture will still be required to test for Ag or RNA to confirm infection. Therefore it is recommended where possible to screen using a plasma or serum sample unless there are concerns about loss to follow up to enable a more complete diagnosis be made.

10. Implementation considerations

Any RDT/ PoC programme in the community should follow the recommendations set out in *Guidelines for Safe and Effective Management and Use of Point of Care Testing in Primary and Community Care (10)*

11. Recommendations for research

List any aspects of the question that have not been answered and should therefore be highlighted as an area in need of further research.

No data are available for the use of RDT/PoC tests in Ireland. Consideration could be given to carrying out research on the performance, feasibility and acceptability of RDTs using blood specimens in an Irish population in a clinical setting.

Review by GDG

Date: 23/02/2017

Recommendation accepted

Consultation feedback and review by GDG

Please see *Report of the consultation process* for feedback received.

No material change to recommendation.

Final recommendation

Recommendation 25

25.1. Where concerns exist about hard-to-reach populations or linkage-to-care then consideration could be given to using approved (e.g. CE marked) rapid diagnostic tests tests/point of care tests (RDTs/PoCTs) on blood specimens.

25.2. If RDTs/PoCTs are introduced into standard clinical practice then a quality assurance programme should be established that addresses internal quality control and external quality assurance.

Quality/level of evidence: low

Strength of recommendation: conditional/weak

References List

1. World Health Organization. Guidelines on hepatitis B and C testing. Geneva: WHO; 2017. Available from: http://www.who.int/hepatitis/publications/guidelines-hepatitis-c-b-testing/en/.
2. Testing for HCV infection: an update of guidance for clinicians and laboratorians. MMWR Morb Mortal Wkly Rep. 2013;62(18):362-5.
3. Khuroo MS, Khuroo NS. Diagnostic accuracy of point-of-care tests for hepatitis C virus infection: a systematic review and meta-analysis. PLoS One. 2015;10(3):e0121450.
4. Drobnik A, Judd C, Banach D, Egger J, Konty K, Rude E. Public health implications of rapid hepatitis C screening with an oral swab for community-based organizations serving high-risk populations. Am J Public Health. 2011;101(11):2151-5.
5. Jewett A, Al-Tayyib AA, Ginnett L, Smith BD. Successful integration of hepatitis C virus point-of-care tests into the Denver Metro Health Clinic. AIDS Res Treat [Internet]. 2013; 2013: 528904. DOI: 10.1155/2013/528904
6. Morano JP, Zelenev A, Lombard A, Marcus R, Gibson BA, Altice FL. Strategies for hepatitis C testing and linkage to care for vulnerable populations: point-of-care and standard HCV testing in a mobile medical clinic. J Community Health. 2014;39(5):922-34.
7. Hayes B, Briceno A, Asher A, Yu M, Evans JL, Hahn JA, et al. Preference, acceptability and implications of the rapid hepatitis C screening test among high-risk young people who inject drugs. BMC Public Health. 2014;14:645.
8. Coats JT, Dillon JF. The effect of introducing point-of-care or dried blood spot analysis on the uptake of hepatitis C virus testing in high-risk populations: a systematic review of the literature. Int J Drug Policy. 2015;26(11):1050-5.
9. Schackman BR, Leff JA, Barter DM, DiLorenzo MA, Feaster DJ, Metsch LR, et al. Cost-effectiveness of rapid hepatitis C virus (HCV) testing and simultaneous rapid HCV and HIV testing in substance abuse treatment programs. Addiction. 2015;110(1):129-43.
10. Working group on point of care testing in primary and community care. Guidelines for safe and effective management and use of point of care testing in primary and community care. Health Service Executive, Pharmaceutical Society of Ireland, Academy of Medical Laboratory Science, Advisory Committee for Medical Devices, Irish Medicines Board, RCPI Faculty of Pathology; 2009. Available from: https://www.icgp.ie/go/library/catalogue/item/01147110-CDA5-40AC-883E5C8D06A6A9E8/.

Appendices

Evidence search and results

International and national guidelines

HCV guidelines identified, reviewed, and quality appraised as described in the National Clinical Guideline.

Grey literature

The following grey literature identified by expert members of the GDG was included for review:

- Guidelines for safe and effective management and use of point of care testing in primary and community care. Working group on point of care testing in primary and community care. Health Service Executive, Pharmaceutical Society of Ireland, Academy of Medical Laboratory Science, Advisory Committee for Medical Devices, Irish Medicines Board, RCPI Faculty of Pathology; 2009. /

Primary literature

The GDG determined that to formulate a recommendation a systematic literature review was required on the role of RDTs/ PoCTs in HCV screening.

PICO

Population: pregnant women attending antenatal services in Ireland
Intervention: screening for HCV using a RDT or PoCT
Comparison: no screening, screening using other laboratory based tests
Outcome: acceptability, uptake rates, detection rates

Search strategy

Sources:

- Medline
- Embase

See table 2 for search terms used in Medline search

Study type/ limits: experimental or observational studies, case studies, case reports; published between 1 January 2010 and 30 June 2015.

Inclusion criteria:

- Low endemicity country
- Reports on prevalence/ incidence in a household contact where there has not been sexual contact with known case and where no other risk factors are apparent; or in a chid of an infected mother where the mode of transmission was not vertical
- HCV status based on blood/ saliva rather than self report
- From 1990

Exclusion criteria:

- Non HCV
- Doesn't report on impact of using POC or RT on testing eg feasibility, acceptabilty, change in uptake
- Other (eg environmental, animal)

- Not POC or RT
- No abstract

Table 2: Search terms used in Pubmed/Medline search

S1	hepatitis c or HCV or hepacivirus or hep c or hepC	Search modes - Boolean/Phrase	75,099
S2	(MM "Hepatitis C+")	Search modes - Boolean/Phrase	41,215
S3	(MM "Hepacivirus")	Search modes - Boolean/Phrase	17,196
S4	S1 OR S2 OR S3	Search modes - Boolean/Phrase	75,099
S5	screen* or early diagnosis or mass screen* or sentinel surveillance or seroepidemiologic stud* or test* or detect* or case finding or universal screen*	Search modes - Boolean/Phrase	4,786,889
S6	(public* or communit* or universal* or widespread or open* or unrestricted or group* or adult*) N3 (screen* or test* or surveillance)	Search modes - Boolean/Phrase	103,227
S7	(MM "Mass Screening")	Search modes - Boolean/Phrase	43,957
S8	(MM "Population Surveillance+")	Search modes - Boolean/Phrase	18,522
S9	(MM "Seroepidemiologic Studies")	Search modes - Boolean/Phrase	185
S10	S5 OR S6	Search modes - Boolean/Phrase	4,790,458
S11	S7 OR S8 OR S9	Search modes - Boolean/Phrase	62,303
S12	S10 OR S11	Search modes - Boolean/Phrase	4,800,801
S13	S4 AND S12	Search modes - Boolean/Phrase	28,034
S14	point of care test* or home based test* or rapid N3 test* or rapid immunoassay test* or rapid antibody test* or self collected test* or over the counter	Search modes - Boolean/Phrase	25,876
S15	(MM "Point-of-Care Systems")	Search modes - Boolean/Phrase	4,823
S16	S14 OR S15	Search modes - Boolean/Phrase	29,624
S17	S13 AND S16	Search modes - Boolean/Phrase	195

Search results

Figure 1: PRISMA flow diagram of review of literature on antenatal HCV screening in Ireland