Hepatitis C Screening Guideline Development Group
Background to recommendation 24: What specimen type should be used for HCV screening?

The purpose of this document is to provide the background information to the formulation of recommendations by the Guideline Development Group (GDG).

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/

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Contents

History of development of the recommendation

Date	Process	Outcome
02/06/2015	Recommendations from quality appraised national and international guidelines reviewed	Agreed to augment evidence from existing guidelines with further literature
20/01/2017	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, SD, ER

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: • **<u>what specimen type (e.g. oral fluid, dried blood spot) should be used?</u>**
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 different specimen types 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: Cost effectiveness
Current Guidelines **WHO, 2016** The use of DBS specimens for anti-HCV antibody serology testing may be considered in settings where: • There are no facilities or expertise to take venous whole blood specimens OR • Rapid diagnostic tests are not available or their use is not feasible OR • There are persons with poor venous access (eg drug treatment programmes, prisons) *Conditional recommendation – low quality of evidence due to risk of bias and inconsistency* The use of DBS specimens to test for HCV RNA for diagnosis of chronic HCV infection may be considered in settings where: • There is a lack of access to sites or nearby laboratory facilities for NAT or provision for timely delivery of specimens to a laboratory OR • There are persons with poor venous access (eg drug treatment programmes, prisons) *Conditional recommendation – moderate quality of evidence due to risk of bias* The guidelines note that there are currently no manufacturers' protocols for the use of DBS with their assays or regulatory approval for the use of DBS samples. Therefore the use of DBS specimens would be considered "off-label". (*WHO 2016 (draft report) Guidelines on hepatitis B and C testing (1)*) **NICE, 2012**

Recommendation: Prison services and drug services should have access to dried blood spot testing for hepatitis C for people for whom venous access is difficult.

Background: While venepuncture samples remain the gold standard, the programme development group (PDG) noted that dried blood spot tests for hepatitis C have a high test sensitivity and specificity and can be useful in certain settings for people with poor venous access and where there may be no facilities or expertise to take venous blood samples. In addition, more staff would probably be able to carry out such tests, so helping to increase the number of people who are tested. The PDG noted preliminary evidence from the Scottish Hepatitis C Action Plan programme suggesting that hepatitis C testing in specialist drug clinics increased after the introduction of dried blood spot testing and wide-scale training of healthcare workers in hepatitis C.

The PDG acknowledged that there is encouraging evidence from pilot schemes where community pharmacists provide dried blood spot testing for hepatitis. Although the evidence is not strong enough to uniformly recommend that all community pharmacists provide this service, the PDG felt that it would be worthwhile considering extending pilot programmes. This extension could be considered for pharmacists already engaged with people at increased risk of hepatitis B and C, such as pharmacists providing needle exchange and NHS health checks.

The PDG recognised that oral fluid testing may be more acceptable to some people because it is less invasive than taking blood from a vein, but that oral fluid testing has a lower sensitivity and specificity than tests for hepatitis B and C performed on blood. If an oral fluid sample was used, a blood sample would then be needed to confirm the initial positive results, and for PCR testing to diagnose chronic hepatitis C.

The PDG identified that there was a lack of evidence on the acceptability of different sampling methods for testing for hepatitis.

(*The National Institute for Health and Care Excellence, Hepatitis B and C: Ways to Promote and Offer Testing to People at Increased Risk of Infection (2)*). HIQA Quality Score 148

SIGN, 2013
Diagnostic testing for HCV should be performed on serum or plasma where possible. Dried blood spot (DBS) testing should be considered as a convenient and cost-effective method of accessing some target populations.
(Scottish Intercollegiate Guidelines Network, Management of Hepatitis C A National Clinical Guideline (3)). HIQA Quality Score 127.7

Literature Review

A review of primary literature was carried out to assess the technical performance of other specimen types – DBS, oral fluid, saliva – and other non-technical aspects such as acceptability, impact on screening rates etc. A time limit was applied and the search was restricted to literature published from 2006 onwards.

Technical performance
17 primary research articles were critically appraised

- 10 considered the performance of DBS samples
  - 1 systematic review (Greenman (4)) which considered DBS samples for detection, quantification, genotyping and storage of HCV RNA
  - 1 study (Kainne Dokubo (5)) which considered DBS samples from finger pricks for detection of anti-HCV and HCV RNA
  - 5 studies which considered DBS samples prepared from whole blood samples
    - Ross et al (6) – DBS from whole blood for anti-HCV and HCV RNA
    - Lee et al (7)- DBS from whole blood for anti-HCV

        - McAllister et al (8)– DBS and eluates from whole blood for assessment of long term stability at different temperatures, with and without dessicant.
        - Croom et al (9) - DBS from whole blood for anti-HCV
        - Marques et al (2016)(10) - DBS from whole blood for anti-HCV, quantitative in-house PCR, and qualitative PCR.
    - 3 studies which considered DBS from finger-prick or venipuncture
        - Marques et al (2012)(11) - DBS from whole blood collected via finger prick or venepuncture for anti-HCV
        - Brandao et al (12) - DBS from whole blood collected via finger prick or venepuncture for HCV AgAb
        - Tejada-Strop et al (13)- DBS from whole blood (varying sources - finger-prick or venepuncture) for anti-HCV detection, HCV RNA quantification, HCV genotyping. Performance in both freshly prepared DBS and stored DBS (stored at -20^{o} with dessicant for 5 years) assessed.
- 2 considered both DBS and OF samples
    - Rice and Abou-Saleh(14)– DBS from finger-prick and saliva for anti-HCV
    - Larrat et al (15) - DBS (from finger prick) and oral mucosal transudate (OMT) via OraSure collection device for HCV AgAb
- 5 considered OF/saliva samples
    - Visseaux et al (16)– anti-HCV in saliva collected with Salivette kit
    - Cruz et al (17)- anti-HCV in saliva collected by spitting or with Salivette kit
    - Moorthy et al (18) - anti-HCV in saliva collected with OmniSal collection device
    - Gonzalez et al (19)– anti-HCV in oral fluid collected with OraSure collection device
    - Amado et al (20)- anti-HCV in oral fluid collected with OraSure collection device

The systematic review by Greenman et al (4)included 9 studies:

- 8 studied DBS and one studied dried serum.
- 4 studied end-point detection limits for HCV-RNA. RNA was detected by DBS in 100% of HCV-positive samples with serum viral loads as low as 150–250 IU/mL up to 4,830-24,160 IU/ml.
- Four studies provided data sufficient to calculate the sensitivity, specificity, positive predictive value and negative predictive value of DBS in HCV RNA detection against the standard of paired plasma samples; one study provided only enough information to measure sensitivity. Sensitivity ranged from 93.8–100%, specificity ranged from 94.0–100%, PPV ranged from 96.1-100, and NPV ranged from 90-100%.
- 4 examined stability of HCV-RNA in DBS samples and found differing results.
- 2 measured concordance between genotype and subtype determination by DBS and whole plasma and found 100% concordance.
- Five studies reported the proportion of HCV RNA-positive samples that could be genotyped. Four were able to successfully genotype 87.7% to 100% of RNA positive DBS samples.

Additional studies that examined performance of tests on DBS samples found the following:

- In the studies that examined performance of DBS samples in detection of anti-HCV antibodies the sensitivity ranged from 70-98.3% and the specificity ranged from 98.9-100%.
- In the studies that examined performance of DBS samples in detection of HCV RNA the sensitivity ranged from 65.9-97.8% and the specificity in all 4 studies was 100%. The low sensitivity of 65.9% was found in an in-house PCR test that was developed compared to all other studies that modified existing PCR tests. Excluding this in-house PCR test, the sensitivities ranged from 88-97.8%.
- In 2 studies that examined performance of DBS samples in detection of HCV AgAb the sensitivity ranged from 80-98.2% and the specificity ranged from 96-100%.

See accompanying Table 1 for further details

Additional studies that examined performance of tests on saliva / oral fluid samples found the following:

- In the studies that examined performance of saliva / oral fluid samples in detection of anti-HCV antibodies

the sensitivity ranged from 73-93.9% and the specificity ranged from 92.5-100%.

- One study examined performance of saliva / oral fluid samples in detection of HCV AgAb by two assays and the sensitivity ranged from 71.7-94.6% and the specificity ranged from 94.3-100%.

See accompanying Table 2 for further details

Non-technical performance

Coats and Dillon carried out a systematic review of studies that contained quantitative data on the frequency of testing and/or new diagnoses after the introduction of DBS testing of high-risk populations (21). They included six studies in their review (2 RCTs, 2 prospective cohort studies, 1 ecological study and 1 clinical audit). All included studies were judged to have a high risk of bias due to a number of different reasons. Five of the six studies provided evidence that the introduction of DBS testing increased the number of tests, new diagnosis or both. Variable effect sizes were found due to the heterogeneity of the studies included. 1 stepped-wedge cluster RCT demonstrated no effect.

White et al carried out a qualitative study with IDUs and explored the acceptability of three sample collection methods – oral fluid collection, DBS from finger-prick, and venepuncture (22). The study methods used introduced considerable bias. However all three collection methods were found to be highly acceptable. Oral fluid sampling was reported as the preferred method of testing and capillary sampling was the least preferred method.

In a study by Lucidarme et al IDUs were randomly allocated to either screening via venepuncture or via saliva collection (23). The study was not specifically designed to assess impact of different testing methods on outcomes such as acceptability and impact on uptake. Screening rates were significantly higher in the saliva collection arm of the study resulting in a higher proportion of HCV Ab positive diagnoses in the saliva collection arm (10.3% Vs 8.6%).One third of participants randomised to the venepuncture arm of the study could not be tested due to poor venous access. However, venepuncture sampling enabled a greater number of antibody positive patients to be tested for HCV RNA (91% Vs 53%)

Cost effectiveness

Martin et al carried out a cost-effectiveness study of DBS use in prisons and specialist drug treatment services using a dynamic model (24). The compared offering DBS testing in prison or specialist addiction services to the current practice of testing by venepuncture only. A health service perspective was taken and lifetime time horizon used. Costs and utilities were discounted at a rate of 3.5% per year. The model assumed a 3.6fold increase in testing in addiction services and a 2.6 fold increase in testing in prisons based on published studies. They demonstrated that for a £20,000 per QALY gained willingness-to-pay threshold, DBS testing in addiction services is cost-effective (ICER of £14,600 per QALY gained (€19,141 when inflated and converted to Irish Euro)). Under the base-case assumption of no continuity of treatment/care when exiting/entering prison, DBS testing in prisons is not cost-effective (ICER of £59,400 per QALY gained (€77,874 when inflated and converted to Irish Euro)). Results were robust to changes in HCV prevalence. Increasing PWID treatment rates to those for ex-PWID considerably reduces ICER (£4,500 and £30,000 per QALY gained for addiction services and prison, respectively). If continuity of care is >40%, the prison DBS ICER falls below £20,000 per QALY gained.

NICE 2012 Guidelines– additional evidence
Training for dried blood-spot testing in the community resulted in a substantially greater proportion of cases of hepatitis C infection being identified, compared with not offering this blood sampling method. This led to an estimated cost per quality-adjusted life year (QALY) gained of £15,000 (€19,106 assuming cost year was 2012), which is below the threshold of £20,000 generally accepted by NICE as cost effective.
Training prison nurses to undertake dried blood spot testing also increased the proportion of hepatitis C cases

found, compared with not offering this sampling method. However, the cost effectiveness of this training depended on whether the resulting treatment was completed. The baseline scenario considered no continuity of care between prison and the community – in which case the cost per QALY of finding a new case was estimated to be £59,000 (€75,152 assuming cost year was 2012) per QALY and therefore was not cost effective. The estimated cost per QALY of case-finding in prison will be less than £20,000 per QALY gained if there is continuity of care between prison and the community and the treatment rate of people diagnosed in prison is at least 40% of the treatment rate of people diagnosed in the community. Higher treatment rates in the community make prison case-finding more cost effective as long as there is continuity of care.

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.

Technical performance

There is significant heterogeneity between studies. Studies varied considerably in their objectives and methods and tested different assays.

Of the seven studies on saliva/oral fluid/OMT, six assessed the ability to detect anti-HCV and one assessed ability to detect HCV AgAb

Of the 12 studies on DBS, eight assessed the ability to detect anti-HCV, five addressed aspects of HCV-RNA testing, two assessed the ability to detect HCV AgAb, and three assessed issues regarding stability and storage of DBS samples.

Different methods were used for the collection of oral fluid, saliva and DBS samples. The methods for preparing DBS varied eg elution and dilution methods, filter paper disc size, volume of whole blood used etc.

As there are no commercially available tests that are approved for use on DBS or oral fluid/saliva samples all studies applied varying modifications to the manufacturers' instructions.

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

There is significant heterogeneity between studies.

The majority of studies on DBS sample performance demonstrated a high sensitivity and specificity.

The majority of studies on oral fluid samples demonstrated a lower sensitivity

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

Studies used different source populations– general hospital patients, hospital patients with chronic liver disease, acute hepatitis, community IDUs etc.

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

No

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?

Benefits:

- DBS and oral fluid samples are non-invasive and easier to obtain from patients, particularly those with poor venous access. Neither requires trained healthcare professionals and both can be used for self-sampling. Oral fluid sampling avoids and DBS sampling reduces the risk of needle stick injuries.
- DBS samples can be transported without the need for refrigeration and do not require plasma separation within a specified time period.
- DBS sampling may be particularly useful in settings where larger numbers of tests are being done eg prisons, DTC etc

Potential Harms

- Sensitivity of testing on oral fluid samples is lower than acceptable with poor PPV
- Commercial assays have not been validated for use with DBS or oral fluid samples
- Pre-analytical treatment of DBS samples has not been standardised. This could impact on test performance

6.2. What are the likely resource implications and how large are the resource requirements? Consider cost effectiveness, financial, human and other resource implications

Because DBS sampling does not require healthcare professionals trained in venepuncture this method of testing could have positive resource implications both financial and human. However, there could be an impact on lab processing times. Most importantly, in the absence of authorised approval of commercial assays, considerable resources would need to be invested in validation, standardisation, quality assurance and quality control.

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

If authorised quality assured assays existed and staff were appropriately trained for the context in which the tests are used, it is likely that the use of DBS samples would be acceptable to healthcare providers and to patients.
Oral fluid samples for diagnostic purposes should not be acceptable to healthcare providers due to the low sensitivity

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

DBS samples are not currently used in Ireland for HCV screening / diagnostic purposes
There are currently no manufacturers' protocols for the use of DBS with their assays or regulatory approval for the use of DBS samples. Therefore the use of DBS specimens would be considered "off-label".
Therefore challenges with validation, standardisation, quality assurance and quality control

6.5. What would be the impact on health equity?

In the future if a validated quality assured assay was authorised for use with DBS samples, this might enable an increase in screening rates particularly amongst PWID who may have poor venous access, who are a vulnerable patient group and often socially excluded. Therefore the use of DBS could have a positive impact on health equity. However, there are no data from Ireland to indicate that poor venous access represents a current barrier to participation in existing screening programmes or opportunities.

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

The low sensitivity of oral fluid as a specimen type is not considered acceptable.

8. Final Recommendations

√ Strong recommenda□on
□ Condi□onal/ weak recommenda□on

Text:

- Serum or plasma are the preferred specimen types for ccreening and diagnostic testing for HCV infection using quality assured assays.
- Screening and diagnostic testing for HCV infection should not be performed on oral fluid samples due to the low sensitivity and positive predictive value

9. Justification

- HCV testing on DBS samples as recommended by the WHO has a particular role to play in low and middle income countries where laboratory facilities and other relevant infrastructure and services are poor or absent. In a developed, geographically small country such as Ireland these difficulties do not arise.
- No approved (e.g. FDA / CE) assay currently exists for use with DBS specimens
- There are no data in Ireland that indicate that poor venous access is a significant barrier to HCV testing. For most patients venous phlebotomy is required for additional testing for HCV and other clinical indications.
- Where concerns exist about hard-to-reach populations or linkage-to-care then consideration could be given to using approved rapid diagnostic tests

10. Implementation considerations
None
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.

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 15

See Recommendation 14 for MSM attending for sexual health screening.

15.1. HCV testing should be considered part of routine sexual health screening in the following circumstances:

- People who are HIV positive
- Commercial sex workers
- PWID
- If indicated by the clinical history e.g. unexplained jaundice
- When other risk factors for HCV as outlined in this guideline are present*

*See Appendix 1 for a list of risk populations.

Quality/level of evidence: low

Strength of recommendation: conditional/weak

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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

Nil used.

Primary literature

The GDG determined that to formulate a recommendation further information was required on the the use of different specimen types in HCV screening.

PICO
Population: people/ specimens being tested for HCV
Intervention: testing for HCV using different specimen types
Comparison: n/a
Outcome: sensitivity, specificity, predictive value, acceptability, uptake

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 2006 and 30 June 2015

Exclusion criteria:

- Non HCV
- Doesn't report on Impact of using a particular specimen type
- Other (eg environmental, animal)
- No abstract

Table 2: Search terms used in Pubmed/Medline search

		Results
#26	#13 AND #25	198
#25	#15 OR #16	6,171
#24	#13 AND #23	13,375
#23	#15 OR #16 OR #17 OR #19 OR #20 OR #21 OR #22	2,097,434
#22	'saliva'/exp/mj	13,722
#21	'plasma'/exp/mj	35,934
#20	'serum'/exp/mj	42,038
#19	'venous blood'/exp/mj	919
#17	serum OR venous NEXT/1 blood* OR plasma OR finger NEXT/1 stick NEX T/1 blood* OR fingerstick* OR fingerprick* OR finger NEXT/1prick* OR s aliva OR 'whole blood'	2,093,865
#16	'dried blood spot testing'/exp/mj	891
#15	oral NEXT/1 fluid* OR dried NEXT/1 blood NEXT/1 spot*	6,171
#13	#4 AND #12	48,562
#12	#10 OR #11	6,259,250
#11	#7 OR #8 OR #9	338,346
#10	#5 OR #6	6,047,711
#9	'seroepidemiologic studies'/exp/mj	278,516
#8	'population surveillance'/exp/mj	23,329
#7	'mass screening'/exp/mj	61,562
#6	(public* OR communit* OR universal* OR widespread OR open* OR unr estricted OR group* OR adult*) NEAR/3 (screen* OR test* ORsurveillance)	119,205
#5	screen* OR 'early diagnosis' OR mass NEXT/1 screen* OR 'sentinel surveillance' OR seroepidemiologic NEXT/1 stud* OR test* ORdetect* O R 'case finding' OR universal NEXT/1 screen*	6,043,875
#4	#1 OR #2 OR #3	122,920
#3	'hepacivirus'/exp/mj	18,598
#2	'hepatitis c'/mj	50,687
#1	'hepatitis c' OR hcv OR hepacivirus OR 'hep c' OR hepc	122,920

Search results

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