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Uptake of hepatitis C specialist services and treatment following diagnosis by dried blood spot in Scotland

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1 **Abstract**

2

3 **Background**

4 Dried blood spot (DBS) testing for hepatitis C (HCV) was introduced to Scotland in
5 2009. This minimally invasive specimen provides an alternative to venipuncture and
6 can overcome barriers to testing in people who inject drugs (PWID).

7 **Objectives**

8 The objective of this study was to determine rates and predictors of: exposure to
9 HCV, attendance at specialist clinics and anti-viral treatment initiation among the
10 DBS tested population in Scotland.

11 **Study design**

12 DBS testing records were deterministically linked to the Scottish HCV Clinical
13 database prior to logistic regression analysis.

14 **Results**

15 In the first two years of usage in Scotland, 1322 individuals were tested by DBS of
16 which 476 were found to have an active HCV infection. Linkage analysis showed that
17 32% had attended a specialist clinic within 12 months of their specimen collection
18 date and 18% had begun anti-viral therapy within 18 months of their specimen
19 collection date. A significantly reduced likelihood of attendance at a specialist clinic
20 was evident amongst younger individuals (<35 years), those of unknown ethnic origin
21 and those not reporting injecting drug use as a risk factor.

22 **Conclusion**

23 We conclude that DBS testing in non-clinical settings has the potential to increase
24 diagnosis and, with sufficient support, treatment of HCV infection among PWID.

25

26 **Background**

27

28 In Scotland, 0.8% of the population aged 15-59 years had been diagnosed with
29 hepatitis C virus (HCV) antibodies by the end of 2012 [1]. The majority of these
30 infections occur in individuals with a history of injecting drug use [2] and recent
31 estimates suggest that around half of people infected with HCV remain undiagnosed
32 [1]. To tackle the epidemic of HCV in Scotland, the Hepatitis C Action Plan for
33 Scotland was launched in September 2006 [3]. In its initial Phase (September 2006 –
34 March 2008) the Action Plan identified poor venous access amongst people who
35 inject drugs (PWID), along with a shortage of trained phlebotomists, and the long
36 interval between testing and return of results, as barriers to testing and diagnosis of
37 HCV in this population [4]. Dried blood spots (DBS), drops of whole blood from a
38 finger prick dried onto filter paper, provide an alternative to whole blood specimens
39 collected by venipuncture and can overcome the majority of barriers to HCV testing
40 outlined above [5,6,7,8]. As a result of the Action Plan, DBS testing for HCV
41 diagnosis was introduced in Scotland in May 2009. Now that DBS testing is well
42 established in Scotland, the outcomes of DBS testing are quantifiable to give a better
43 understanding of the utility of the DBS approach.

44

45 **Objectives**

46

47 The objective of this study was to determine the proportion of those tested by DBS in
48 Scotland who had been exposed to HCV; of those diagnosed as being currently
49 infected with HCV the proportion attending a specialist clinic and, of those, the
50 proportion who were initiated on anti-viral treatment. Epidemiological information

51 collected alongside the DBS specimens is also analysed to identify predictors of
52 exposure, attendance and treatment initiation amongst this population.

53 **Study Design**

54

55 **Data Sources and Linkage**

56 The Scottish Hepatitis C Clinical Database, held at Health Protection Scotland (HPS),
57 contains clinical follow-up data for HCV-infected patients attending 17 specialist
58 clinics across Scotland. These data include attendance dates, treatment episodes,
59 demographic, clinical, virological, and patient identifiers (date of birth, sex, surname
60 Soundex (a consonant-only phonetic encoding), and forename initial). Data were
61 restricted to individuals on the database on 31 December 2012 and at this date the
62 database contained records for 14,298 individuals with sufficient identifiers for
63 linkage.

64

65 HPS also maintains records on all DBS testing in Scotland since May 2009. The DBS
66 database contains information on dates and result(s) of HCV antibody and reverse
67 transcriptase polymerase chain reaction (RT-PCR) testing, source, ethnicity, risk
68 activitie(s), length of injecting career and limited identifying information (i.e., date of
69 birth, sex, surname Soundex and forename initial). On 31 December 2010 this
70 database comprised records for 1448 specimens relating to 1322 individuals.

71

72 Records from the DBS database (up to 31 December 2010) were deterministically
73 linked to individuals on the HCV Clinical database (to 31 December 2012); a
74 complete match on surname Soundex, gender, DOB, and first initial was required for
75 a successful link.

76

77

78 **Data Analysis**

79 Three main outcomes were analysed: (a) anti-HCV positivity amongst all individuals
80 tested by DBS for HCV since the inception of the DBS testing programme in Scotland
81 (May 2009) to 31 December 2010, (b) first clinic attendance amongst all chronically
82 HCV-infected persons recorded as being tested by DBS for HCV infection between
83 May 2009 and 31 December 2010 and (c) initiation on antiviral therapy amongst the
84 chronically HCV-infected patients attending a specialist clinic. Univariate and
85 multivariate logistic regression modelling was used to examine the association
86 between the covariates sex, age at diagnosis (grouped into < 35years, ≥ 35years),
87 ethnicity (White, Unknown/Non-white), Source of DBS (Community Addiction
88 Team/Harm Reduction, Other) and time since onset of injecting (≤10years, > 10years,
89 Not Known (PWID), Non-PWID) and the outcomes: ‘HCV antibody positive’ (Table
90 1), ‘first clinic attendance within 12 months of diagnosis by DBS’ (Table 2) and
91 ‘initiation on antiviral therapy within 18 months of DBS specimen collection’ (Table
92 3). For the latter analysis the variable ‘Risk Factor’ (Current PWID, Past PWID,
93 Non-PWID/Unknown) was also included. For the Risk Factor variable data collected
94 on length of injecting career (including age of first and last injection) was used, where
95 available, to categorise individuals as past PWID and present PWID, with any
96 individual giving a date of last injecting drug use as five or more years prior to the
97 DBS specimen collection date classified as a past PWID.

98

99 All analysis was carried out in R 3.0.1 [8]. Exact p-values are provided except where
100 $P < 0.001$.

101 **Results**

102

103 In 2009/10 DBS specimens were collected from 1322 individuals in Scotland for
104 HCV screening. Of these individuals 55% (n=728) were seropositive for antibody to
105 HCV, and approximately two-thirds (65.4% (n=476)) had an active HCV infection
106 (Figure 1). Table 1 presents characteristics of the overall study sample, according to
107 HCV antibody prevalence. The majority (70%) were males, although HCV antibody
108 prevalence in both sexes was equal at 55%. The average age of all DBS tested
109 individuals was 36, with 45% of individuals falling into the < 35yrs age category and
110 55% into the \geq 35yrs category. Antibody prevalence was significantly higher in the
111 older age category compared to the younger; 64% (95% CI: 60 – 67%) and 45% (95%
112 CI: 41 – 49%) respectively. White was the main ethnicity (82.8%), the remainder
113 being of unknown (16.5%) or non-white (0.7%) ethnicity. Most individuals (89.3%)
114 were tested in a community addiction team or harm reduction setting as opposed to
115 other settings (hospital (3.8%), GP (1.7%), prison (0.6%) or private (4.6%)).

116

117 **Odds of HCV antibody**

118 Multifactorial logistic regression analysis found age to be related to odds of antibody
119 positivity, with those aged \geq 35 years significantly more likely (AOR=1.93, 95%
120 CI:1.51 – 2.47) than those aged < 35 years to be antibody positive. The adjusted odds
121 ratio of ethnicity was also positively associated with prevalence. Individuals who
122 were recorded as being of white ethnic origin being more likely (AOR=2.00, 95% CI:
123 1.42 – 2.85) to be antibody positive as those of unknown/non-white ethnic origin.

124

125 PWID are well known to be at increased risk of infection with hepatitis C, particularly
126 those with longer injecting histories. The majority of individuals (85.6%) tested by
127 DBS reported being/having been a PWID; those who did not report injecting drug use
128 as a risk factor were less likely to be antibody positive (AOR=0.28, 95% CI: 0.17 –
129 0.39) than those who had commenced injecting in the previous ten years. There was a
130 marked increase in prevalence between individuals who had injected for 10 years or
131 less (46.8%) and individuals with injecting histories of over 10 years (80.0%). This
132 translated into a 3.6-fold increased odds of HCV exposure for the individuals with
133 injecting histories of over a decade (AOR=3.58, 95% CI: 2.36 – 5.45) in the adjusted
134 analysis. Finally, although not significant in the multifactorial analysis, individuals
135 tested in a community addiction clinic/harm reduction setting (n=1180) were more
136 likely (OR=1.84, 95% CI: 1.30 – 2.63) to be positive for antibody to HCV as those
137 tested in other settings in the univariate analysis (Table 1).

138

139 **Attendance at Specialist Hepatitis Clinics within 12 months of DBS specimen.**

140 Of the 728 individuals known to be antibody positive there were 476 (65.4%)
141 individuals with an active HCV infection as confirmed by RT-PCR. Linkage of these
142 individuals to the Hepatitis C Clinical Database showed that 202 (42.4%) had ever
143 attended a specialist hepatitis clinic, and 31.9% (n=152) within 12 months following
144 collection of their DBS specimen (Figure 1). For 7.8% (n=37) of individuals a date of
145 attendance prior to the DBS specimen date was also found.

146

147 Univariate analysis did not show any significant relationship between the likelihood
148 of attendance at a specialist hepatitis clinic within the twelve months following
149 diagnosis by DBS and any of the examined variables. However, multifactorial

150 logistic regression found a significant relationship between age, risk factor status and
151 ethnicity and attendance at a specialist clinic within 12 months. Individuals aged 35
152 or older were more likely (AOR=1.49, 95% CI: 1.05-2.13) than those aged <35 years
153 to attend a treatment clinic within 12 months of DBS diagnosis. Individuals who were
154 recorded as being of a white ethnic background were also more likely (AOR=2.85,
155 95% CI: 1.57-5.58) to attend a clinic within 12 months as those of a unknown/non-
156 white ethnic background, and there was also a significantly reduced likelihood
157 (AOR=0.32, 95% CI: 0.13 – 0.71) of attendance at a clinic within 12 months for
158 individuals with a non-PWID risk factor (Table 2).

159

160 **Initiation on anti-viral therapy within 18 months of DBS specimen date**

161 Of the 202 individuals recorded as attending a specialist hepatitis clinic following
162 collection of a DBS specimen in 2009/10, 66 individuals (32.7%) were recorded
163 beginning anti-viral therapy up to the end of 2012. For 18.3% (n=37) of individuals
164 anti-viral therapy was commenced within 18 months of having the DBS specimen
165 collected (Figure 1). Following logistic regression analysis there was no significant
166 association with the likelihood of receiving treatment within 18 months post DBS
167 testing and any of the variables examined in this analysis (Table 3).

168 **Discussion**

169

170 Previous studies have demonstrated the effectiveness of DBS in terms of test uptake
171 amongst PWID [5,6,7,8]. To our knowledge, this is the first study to report on the
172 performance of DBS testing in terms of attendance at specialist clinics and treatment
173 initiation. Overall, we found that of the 476 individuals with active HCV infection,
174 tested by DBS in 2009 and 2010, 31.9% had attended a specialist clinic within 12
175 months of their specimen collection date and, of these, 18.3% had begun anti-viral
176 therapy within 18 months of their specimen collection date.

177

178 To understand how these figures compare to overall HCV diagnosis in Scotland we
179 can relate our findings to a recent analysis which reviewed similar outcomes, across
180 an overlapping time period, in all new HCV diagnoses in Scotland from 1996
181 onwards. The authors report that, of the 1364 individuals newly diagnosed with
182 chronic HCV in Phase II of the Scottish Hepatitis C Action Plan (1 May 2008 to 31
183 December 2010), 44.5% attended a specialist hepatitis clinic within 12 months of
184 being diagnosed and 32% were initiated on anti-viral treatment within the 12 month
185 period following first clinic attendance [10]. Comparing these figures shows that
186 attendance at specialist hepatitis clinics is lower in the DBS tested population at the
187 12 month follow-up point (31.9%) and, although not directly comparable, there also
188 appear to be lower rates of initiation onto anti-viral therapy in the DBS tested
189 population. The populations are not entirely analogous, most notable is that the
190 McDonald et al (2013) study included only new HCV diagnoses whereas this analysis
191 included all diagnoses; among whom there was evidence of prior engagement with
192 specialist services (Figure 1). Since prior knowledge of HCV status may influence

193 the probability of attendance and treatment this may account for some of the variation
194 between the studies. Finally, in our population, of those chronically infected with
195 HCV, 95.4% reported having been/being a PWID and 92.6% were tested at a
196 drug/counselling clinic, compared to 41.9% and 9.7% of the newly diagnosed
197 population. Thus the DBS diagnosed population may well represent a more chaotic
198 group of individuals, involving those who continue to use and inject drugs, which
199 would help to explain the poorer attendance and treatment outcomes amongst this
200 population. Treatment of current PWIDs is still considered problematic by some
201 medical professionals due to concerns over adherence to treatment regimes, medical
202 and psychiatric co-morbidities, psychosocial issues and risk of re-infection [11].
203 However, there is growing evidence to show that, given adequate support, good
204 treatment outcomes can be achieved among people who continue to inject drugs
205 [12,13].

206

207 Looking within our DBS-tested population, logistic regression analysis showed that
208 attendance at specialist hepatitis clinics within 12 months of the DBS specimen
209 collection date was significantly reduced amongst individuals aged less than 35 years
210 and those of unknown/non-white ethnic origin. The significance of the latter finding
211 is unclear as the majority (>98%) of individuals in this category were of unknown
212 ethnicity. We also found that those in the non-PWID risk factor category are
213 significantly less likely to attend a clinic within 12 months of their DBS collection
214 date, despite being chronically infected with HCV. The basis of this difference is
215 unclear but may reflect the high proportion of PWID in our study and the emphasis of
216 this risk factor amongst healthcare professionals working in DBS testing settings.
217 Awareness of these demographic trends amongst healthcare professionals may enable

218 targeted post-test discussion. This analysis did not find any significant association
219 between the variables examined and the likelihood of treatment initiation which may
220 be due to the small sample size and, additionally, our analysis did not have the scope
221 to include the physical, psychological and social factors involved in the decision to
222 treat individuals, and/or willingness to undergo treatment, which have been found to
223 be significant in other studies [14, 15,16].

224

225 DBS testing was recently estimated to be cost-effective in addiction services settings
226 in the UK at an estimated £14,600 per quality adjusted life year (QALY) gained [17].
227 The model was based on 35% of PWID being successfully referred from testing
228 services to secondary care and 5.5% of referred PWID being treated within 2 years.
229 The latter variable was based on the assumption that 1% of infected PWID are treated
230 within 2 years, or 5.5% of those who attended referral. The authors note that the
231 treatment parameter was a critical factor in assessing the cost-effectiveness of DBS
232 testing since higher treatment rates prevent disease transmission thereby increasing
233 the cost-effectiveness of case-finding interventions. Whilst referral rates in our study
234 are similar to those estimated in the model, we have found a much higher proportion
235 of individuals in secondary care being treated; up to a third within 4 years of their
236 DBS specimen and 18% within 18 months of their DBS specimen. Although a
237 proportion of our sample were determined to be past-PWID, for whom treatment rates
238 are higher, 86.2% of the PWID with an active HCV infection had injected within the
239 past five years. As such these findings have great bearing on the cost-effectiveness of
240 DBS testing which was estimated to drop to £4500 per QALY if 50% of referred
241 PWID initiated treatment within 2 years [17].

242

243 Our findings are further evidence of the utility of DBS testing in reaching the
244 populations most at risk from HCV infection and engaging them with specialist
245 hepatitis services. Recent advances in HCV treatment, with the introduction of triple
246 therapy as a standard treatment regime, has significantly improved the rates of
247 sustained virological response [18] and the prospect of interferon-free treatment
248 regimens makes the possibility of an all-oral therapy for HCV conceivable [19,20].
249 Such advances will make treatment a more tolerable therapy and also open the
250 possibility of treatment in the community setting; both of which may facilitate greater
251 uptake in the DBS-tested population in the future. In anticipation of these changes in
252 HCV therapy, and the accompanying possibilities for treatment expansion, the use of
253 DBS should be supported and expanded to maximise engagement with this
254 population.

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257 Plan for Scotland. We would also like to thank Stewart Robinson and Hazel Paterson
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259 **Conflicts of Interest**

260 Funding: This work was funded by The Scottish Government as part of the Hepatitis
261 C Action Plan for Scotland.

262

263 Competing interests: Peter Hayes has received payment from Gilead , MSD and
264 Janssen and Roche

265

266 Ethical approval: Epidemiological data is collected on the laboratory request form and
267 returned along with the dried blood spot specimen to the testing laboratories. All data
268 is handled in accordance to local NHS governance regulations. DBS specimens are
269 always collected with informed consent and the patient is under no obligation to
270 supply any further information along with the specimen. Patients are made aware that
271 any epidemiological information they do provide is held as anonymous surveillance
272 data and will be used for auditing, public health monitoring etc.

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