Hepatitis C Screening Guideline Development Group
Background to recommendation 20: General population or birth cohort 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 that international guidance and literature alone would not be sufficient to address this question. A review of Irish epidemiology required.
14/12/2016	GDG subgroup meeting to undertake considered judgement process	Formulation of recommendation
24/01/2017	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 of meeting: 14/12/2016
Attendees: ER, PF, LT, CDG, OC, JL, SD

Table 1: Considered judgement form – General population

1. What is the question being addressed? Present PICO if relevant
Q2. Who should be offered screening for Hepatitis C? **e. Should there be screening of the general population?**
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)
Recommendations of existing guidelines were initially reviewed. As this initial review, and evidence from the economic literature review (see below), showed that birth cohort screening is generally preferable to general population screening, the GDG subgroup determined to focus on birth cohort screening, and not to consider general population screening further.
3. What is the body of evidence? Source of evidence: (tick all that apply) Guidelines √ Primary literature □ Other √ ; specify: _cost-effectiveness literature
Studies identified in a preliminary search on general population screening were typically single centre studies in specific settings rather than a true general population. Given this, along with the recommendation of the WHO Guideline on hepatitis B and C testing outlined below and the economic literature on general population screening, general population screening is unlikely to be supported over birth cohort screening. Further review of primary literature on general population screening was therefore not undertaken. WHO guidelines for the screening, care and treatment of persons with chronic hepatitis C infection recommend that HCV serology testing be offered to individuals who are part of a population with high HCV seroprevalence or who have a history of HCV risk exposure/ behaviour (1) The WHO Guideline on hepatitis B and C testing concluded that general population screening was generally not cost effective outside specific settings with high general population prevalence (2). The guideline development group considered that one-off birth cohort screening would be more widely applicable. The GDG described the risk that where the epidemic is largely concentrated to a specific birth cohort or other demographic group, that attempting to screen the general population might dilute the testing effort and result in fewer cases being identified. They made only a conditional recommendation to support consideration of general population screening in intermediate and high prevalence settings. A systematic review by *Coward et al.* evaluated five studies which examine d the cost effectiveness of general population screening. Studies were the United States, the Netherlands and Egypt and conducted between 2001 and 2013 (3).The findings of the studies ranged from £66.5 to £62452 per quality adjusted life year gained (QALY). The study with the low cost per QALY was from Egypt, a high prevalence country. Amongst the studies included in the systematic review: a study from the Netherlands found that a campaign using advertising aimed at the general population was not cost effective (4). When a support programme for primary care was added to the campaign an ICER of €11,297 per QALY was estimated. In the US Eckman et al found general population to be cost effective with an ICER of$47276 per QALY based on modelling in a hypothetical population with a prevalence of 1.4% (5). They reported that screening remained cost-effectiveness once the prevalence remained above 0.84%. Coffin et al found general population screening to be cost-effective compared to no screening, but it was dominated by birth cohort screening (6). Coward et al report that prevalence was the main source of variation between the study results.

Table 2: Considered judgement form – Birth Cohort

4. What is the question being addressed?
Q2f. What is the role of birth cohort screening?
5. 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)
In order to adequately address this question it was that felt that a review of other guidelines and published literature alone would not be sufficient as any recommendation on birth cohort screening would need to be based on the epidemiology of hepatitis C virus (HCV) in Ireland. In order to take account of the Irish context, the following approach was taken: • The methodology used in US in making their recommendation was summarised • A literature review was carried out for published studies describing the experience of the implementation of this recommendation in the USA • Available epidemiological information on HCV in Ireland was reviewed, including results from a recent seroprevalence study. • A literature review was carried out to identify relevant studies from other countries that had considered the option of HCV birth cohort screening • An economic literature review was carried out The results of the above are outlined in the briefing paper in appendix 1.
6. What is the body of evidence? Source of evidence: (tick all that apply) ✓ Guidelines ✓ Primary literature ✓ Other; specify: Economic literature; surveillance data; Irish prevalence study
See briefing paper.
7. What is the quality of the evidence? To be considered if primary literature was reviewed (also apply where appropriate to guidelines)
7.1. 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.
N/A
7.2. 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
N/A
7.3. Generalisability – are the patients in the studies similar to our target population for this guideline? is it reasonable to generalise
See briefing paper.
7.4. Applicability - Is the evidence applicable to Ireland? Is the intervention/action implementable in Ireland?
N/A

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

N/A

8. Additional information for consideration

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

See briefing paper.

8.2. Relevant national policy/strategy/practice

Nothing relevant

8.3. Epidemiology in Ireland if available and applicable

See briefing paper.

9. Potential impact of recommendation

9.1. 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:

- Linkage to care and treatment will result in improved quality of life for detected cases.
- The offer of screening also provides an opportunity to raise awareness and educate on hepatitis C.
- Promotion and further normalisation of testing may improve uptake overall and reduce stigma around hepatitis C.
- Detection and treatment of undiagnosed cases will reduce the risk of transmission to others
- There is robust Irish epidemiological data available on which to base the selection of an appropriate birth cohort.
- The "birth cohort" concept is already in conversation amongst professionals and is understood. This could be built on to aid implementation if recommended.
- The approach would detect some those who would not be tested through other screening strategies or who do not have an identified risk factor.
- This approach may remove stigma as a barrier for coming forward for screening.
- It would remove any stigma related to having to ask about risk factors.

Harms:

- The yield is uncertain. Those who are most likely to be negative may be those who present for screening.
- There would be an opportunity cost. The resources could be spent on other aspects of HCV screening and care to possibly greater benefit.
- Diversion of focus and resources away from other risk groups where support is needed to ensure screening and linkage to care occurs.
- In Ireland the proportion of people with hepatitis C who have no identified risk factor is not known. The US recommendation was influenced by knowing that approximately 30% of diagnosed patients did not have an identified risk factor. The high prevalence in the identified age group in Ireland (30-45 years) may be due to the fact those who were PWID at the time of peak incidence of HCV in Ireland are within this age cohort, rather than there being a large cohort of people with no idenitified risk factor, or who do not recall a possible exposure.

- If there are clear pathways to care and treatment available, there is limited foreseeable harm for a person knowing they are infected.
- False positives. The rate of false positive screening results depends on the population being screened. In high risk populations false positive rates are acceptable. However, in low risk populations the positive predictive value of the screening test decreases and may not be acceptable. False-positive test results incur costs and can also cause psychological harm. Confirmatory testing reduces the false-positive rate but increases the cost.
- Detection of cases who may not yet be eligible for treatment may lead to frustration and anxiety.
- Detected cases may suffer from stigmatisation.

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

The resources required to implement screening of a birth cohort will be large. Irish data, points to the highest prevalence being in those aged 30 to 45 years. There are over 1.5 million people within this cohort in Ireland.
Economic studies have shown that for the birth cohort screening to be cost effective high uptake is required. In addition to the costs of testing, communicating the need for testing to this age cohort and marketing to ensure a high uptake would also be costly.
There is no service in place at present through which this screening would take place. It would be a huge burden to general practice to screen this number of patients.
If only opportunistic screening occurred for those attending a healthcare service, those most likely to be positive may not be screened.
A birth cohort screening programme may also require a system to ensure multiple repeat screening (which would increase costs) does not occur e.g if a default opt out testing system was implemented in EDs.

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

- It is uncertain if it would be acceptable to the potential birth cohort.
- It may not be acceptable to some healthcare professionals given the pressures on services and funding cuts in other areas.
- The prevalence is highest amongst males in the East but it may not be acceptable to screen only males or only in one geographical area.

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

Implementation of birth cohort screening may be difficult. There is no service at present that could easily offer screening to those eligible. If screening was to be through GPs a contract and payment would need to be negotiated even if the recommendation was acceptable to GPs.
The programme would also require an information and marketing campaign and possibly an information telephone service to answer queries.

9.5. What would be the impact on health equity?

A potential negative impact is that birth cohort screening may not reach those most at risk. The worried well may be more likely to present for screening rather than those most at risk. Also, the huge cost may divert resources away from ensuring other risk groups are screened and linked into care and treatment.
A potential positive impact is that people who may not otherwise be offered screening based on assumptions of healthcare workers on their risks may be screened and detected.

The principle of proportionate universalism1 should underpin the recommendations and the implementation of the guideline in order to have a positive impact on health equity.

[1] Proportionate universalism is the resourcing and delivering of universal services at a scale and intensity proportionate to the degree of need.
http://www.healthscotland.com/documents/24296.aspx

10. 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

Recent advances in treatment options for hepatitis C make treatment more acceptable and more successful. Treatment with the new DAAs which are now available results in cure in the majority of patients with shorter duration of treatment and less side effects than previous treatments. However at present the cost of these treatments is high.

Screening enables early detection, referral for assessment and treatment where indicated. Without screening cases may go undetected for a considerable length of time due to the asymptomatic nature of HCV infection. Individuals often do not present until symptomatic, which is usually indicative of severe liver damage. Early treatment and cure will confer personal, social, and economic benefits. Early treatment and cure will also reduce the risk of transmission to others. A treatment programme exists in Ireland allowing detected cases access treatment.

While birth cohort screening may identify cases not otherwise identified and may be cost effective, the cost of the programme would be large. The effectiveness of birth cohort screening would depend on uptake which is not known at present. The cost would be large for uncertain benefit.
It may be a better use of resources at present to ensure other risk groups are appropriately screened and linked to care and treatment.

11. Final Recommendations

□ Strong recommenda□on
√ Conditional/ weak recommendation

Text:

Triangulation of data from a number of sources identified the birth cohort between 1965-1985 as being most affected by hepatitis C infection in Ireland.

However, birth cohort screening cannot be recommended at present due to the likely huge cost implications and uncertain benefit. Such a programme would require a full health technology assessment (HTA) and approval of funding prior to being considered.

Birth cohort screening should be considered if a HTA shows it to be cost effective and affordable in the Irish context.

12. Justification

A number of data sources indicate that the prevalence of HCV infection in Ireland is highest in those born between 1965 and 1985. Thirty one percent (n=1,426,156) of the Irish population were born between 1965 and 1985. The resources required to implement screening of this number of people would be huge.
A recent Irish study found the prevalence of hepatitis C to be highest amongst males resident in the East. A recommendation to screen only this group would still result in 250,000 people being eligible for screening which would still require huge resources to implement. In addition, screening of only one gender or one geographical region may not be acceptable.
The implementation of any birth cohort screening recommendation would require huge resources and the impact is uncertain as it will be influenced by the uptake of screening.
There is also concern that birth cohort screening would divert resources away from screening and supporting linkage to care for other vulnerable risk groups. A proportion of this cohort may be reached by the strengthening of screening strategies for other risk groups.

A HTA and comprehensive budget impact should be undertaken prior to further consideration of birth cohort screening. This HTA should also include the costs of implementation of birth cohort screening beyond testing costs such as the costs of marketing and communication as recommended by systematic reviews of birth cohort screening.
13. Implementation considerations
Implementation of birth cohort screening should only be considered after a comprehensive health technology assessment and securing of resources.
14. 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: 24/01/2017

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 17

17.1. Birth cohort screening cannot be recommended at present due to the likely substantial cost implications and uncertain benefit. Such a programme would require a full health technology assessment (HTA) and approval of funding prior to being considered.

17.2. Birth cohort screening should be considered if a HTA shows it to be cost effective and affordable in the Irish context.

Quality/level of evidence: moderate

Strength of recommendation: conditional/weak

References List

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Appendices

Briefing paper for the Guideline Development Group

A key question the guideline is to address is if HCV screening should be recommended for a particular birth cohort of the population.

In the United States, a recommendation was made in 2012 by CDC to offer one-time screening for HCV infection to adults born between 1945 and 1965, in addition to screening in persons at high risk of infection. In order to provide the background to consider if such a recommendation would be appropriate in an Irish population, the following approach was taken:

- The methodology used in US in making their recommendation was summarised
- A literature review was carried out for published studies describing the experience of the implementation of this recommendation in the USA
- Available epidemiological information on HCV in Ireland was reviewed, including results from a recent seroprevalence study.
- A literature review was carried out to identify relevant studies from other countries that had considered the option of HCV birth cohort screening
- An economic literature review was carried out

United States recommendation on birth cohort screening

1. The Centers for Disease Control and Prevention (CDC) recommendation: Adults born during 1945–1965 should receive one-time testing for HCV without prior ascertainment of HCV risk.[1]
2. The United States Preventive Services Task Force (USPSTF) recommends screening for hepatitis C virus (HCV) infection in persons at high risk for infection. The USPSTF also recommends offering 1-time screening for HCV infection to adults born between 1945 and 1965.[2]
3. The American Association for the Study of Liver Diseases (AASLD): One time HCV testing is recommended for persons born between 1945 and 1965, without prior ascertainment of risk.[3]

Methodology used to make this recommendation in the United States

- In the United States, an estimated 1-1.5% of the population is living with hepatitis C infection.[4]
- Source and description of prevalence data: National Health and Nutrition Examination Survey (NHANES) data, 1999-2002[4]. They took a representative sample of the US civilian, non-institutionalised population. Of 21,509 participants 6 years or older, 17,548 were interviewed and 15,079 people gave a blood sample suitable for anti-HCV testing. They found an anti-HCV prevalence of 1.6% (1.3-1.9%). This is likely to be an underestimate of anti-HCV prevalence as the sample did not include homeless or incarcerated people. Seventy nine percent were subsequently tested for hepatitis C RNA, 80% tested positive. After accounting for untested specimens the nationwide prevalence of HCV RNA was 1.3% (1-1.5%).
- Undiagnosed fraction: 45-85%.[1] Of the estimated 2.7–3.9 million persons living with HCV infection in the United States, 45%–85% are unaware of their infection status; this

proportion varies by setting, risk level in the population, and site-specific testing practices. Four studies were cited for reaching this estimate.

- CDC unpublished surveillance data, 2012: 45% of cases reported no known exposure
- 1999-2008 NHANES data: 1945-1965 birth cohort includes 27% of the US population and 76.5% of cases of HCV. There was an anti-HCV prevalence 3.25% in this birth cohort, 5 times higher than adults born outside these years. This reflects high hepatitis C incidence in the 1970s and 1980s[6]
- They considered other birth cohorts which were estimated to include between 7 and 87% of all chronic HCV cases. Birth cohort 1945-1970 would be likely to include 87% of cases of HCV, but an additional 20 million people would have to be screened, by extending the cohort to 1970.
- Data collected through a series of 12 consumer focus groups in three different U.S. cities demonstrated that the 1945–1965 birth cohort is a recognized subpopulation known as the "baby boomers;" familiarity with this subpopulation and the term used to describe it likely would facilitate adoption and implementation of the recommendation.
- Methods behind decision: large multi-disciplinary working group, systematic reviews of literature, evaluation of economic/resource implications, expert group graded all the information and reached a decision regarding the strength of recommendations. Guidelines were peer reviewed by experts and public comment invited.
- They compared risk based screening and birth cohort screening with respect to number of tests, number of cases HCV identified, number of patients treated, number of patients achieving SVR, number of cases of cirrhosis, number of cases of HCC, number of liver transplants, number of liver related deaths.
- The cost effectiveness studies used in this were based on earlier treatment regimes, but birth cohort screening was found to be cost-effective. "Only two U.S.-based studies specifically examined the cost effectiveness and resource implications of birth-year-based HCV testing linked to HCV care and treatment; both studies found the interventions to be cost effective. These studies, which evaluated slightly different definitions of birth cohort, compared birth-cohort testing and treatment with the status quo of risk- and medical indication-based testing recommendations; both studies demonstrated nearly identical cost-effectiveness results. The first study, which defined the birth cohort as persons born during 1945–1965, estimated a cost per quality-adjusted life year (QALY) gained of $35,700 on the basis of a 12-week, response-guided course of telaprevir and PR; cost per QALY was an estimated $15,700 when assuming treatment with PR alone. The second study defined the birth cohort as persons born during 1946–1970 and estimated a cost per QALY gained of $39,963 for patients treated with telaprevir in addition to PR."[1]

Studies of the implementation of birth cohort screening in the US

Many studies have been published describing the results of implementing the 2012 HCV birth cohort screening recommendations in the US. High prevalences of HCV antibody and RNA positivity have been commonly found (>10% antibody positive). However, many of the study settings have been in urban, socially deprived areas with known high risk populations, which would not be representative of the general population. Although birth cohort screening avoids the need to ask about risk factors and captures people who may not be aware that they had past risk factors for HCV, the yield may be considerably lower in healthcare settings serving lower risk populations.

Electronic flags in patient databases were associated with better uptake of screening. Same-day RNA testing using the sample drawn for serology, and assisted linkage to care, were associated with better follow up of antibody positive patients (higher rates of HCV RNA testing, better linkage to specialised hepatology care and assessment for treatment). (References available on request).

WHO guidelines on hepatitis B and C testing 2016 – draft unpublished[5]

The World Health Organization (WHO) Guideline on hepatitis B and C testing (awaiting publication) states that the best approach to screening will depend on a country's unique HCV epidemiology. The WHO Guidelines Development Group concluded that whenever there is an easily identified demographic group that has a high HCV prevalence (e.g. all individuals born in a certain time period), routine testing for HCV within that cohort, i.e. "birth cohort" testing will likely be cost-effective and should be considered. This will largely apply to those countries where routine screening of the blood supply for HCV in the 1990s and improvements in injection safety practices have since removed the exposure risk. A conditional recommendation was made mainly because of low quality of evidence.

Benefits:

1. Recent studies in the US showed birth cohort screening to be cost-effective when compared with risk-based screening. While typically identified as being the infection pattern in North America and Europe, many countries have at least some component of "birth cohort" epidemic in their HCV epidemiology, and therefore "birth cohort" testing is likely to be cost-effective in most settings.
2. A key advantage of this generally one-off screening approach is that it avoids the need to identify specific behavioural risks as the basis for screening, because providers are often not skilled at identifying high-risk behaviours, and individuals may not remember that they received a blood product, or admit to previous risk-taking behaviour on direct questioning.

Risks: However, more recent data suggest that a significant proportion of the HCV-infected population is not captured as part of birth cohort screening. A further challenge is that this approach requires reliable data on both the age distribution of the population and prevalence according to age, which is not available in most countries.

Epidemiological information on HCV in Ireland

As described above, in making the recommendation in USA, data were accessible from NHANES with HCV testing of a large sample representative of the general population. In Ireland, until recently, HCV seroprevalence studies had been carried out only in selected high-risk or localised populations, and in antenatal women, but there had been no national HCV prevalence studies in the general population. A national cross sectional study has recently been completed using residual sera available in the National Virus Reference Laboratory – the results of this are described below. Information is available from the computerised infectious disease reporting system (CIDR) on HCV notifications nationally since HCV became a notifiable disease in 2004. However, these represent only diagnosed cases of HCV. No comprehensive studies have been carried out in Ireland to estimate the undiagnosed fraction.

No cost-effectiveness studies have been carried out in Ireland on the cost-effectiveness of HCV screening in different populations/settings.

HCV notification data in Ireland

The number of notifications of HCV in Ireland annually is shown in figure 1. 66% of notifications were in males. More than two thirds of cases are notified in HSE East. Where risk factor data are available, over 80% of HCV notifications are in people who inject drugs.

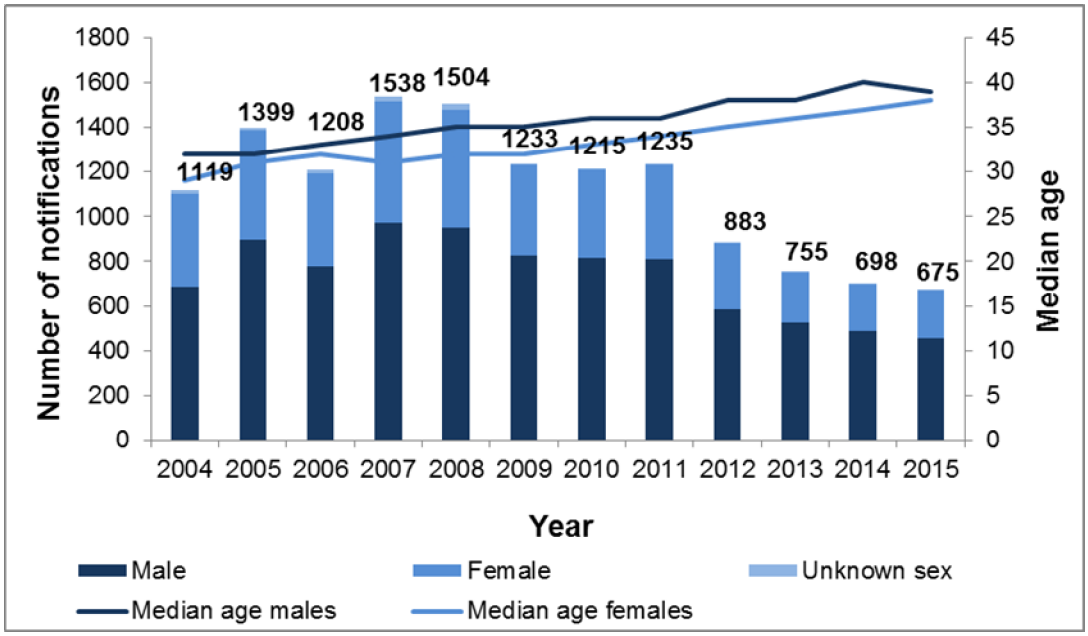

Figure 1. Number of notifications of hepatitis C, 2004-2015, by sex and median age

Figures 2 and 3 show the distribution of notified (diagnosed) cases of HCV by birth year and age at notification for the years 2004 to June 2016. Of these notifications, 72.5% fall into the age group 1965-1985, compared to 31.1% of the population falling into this age group.

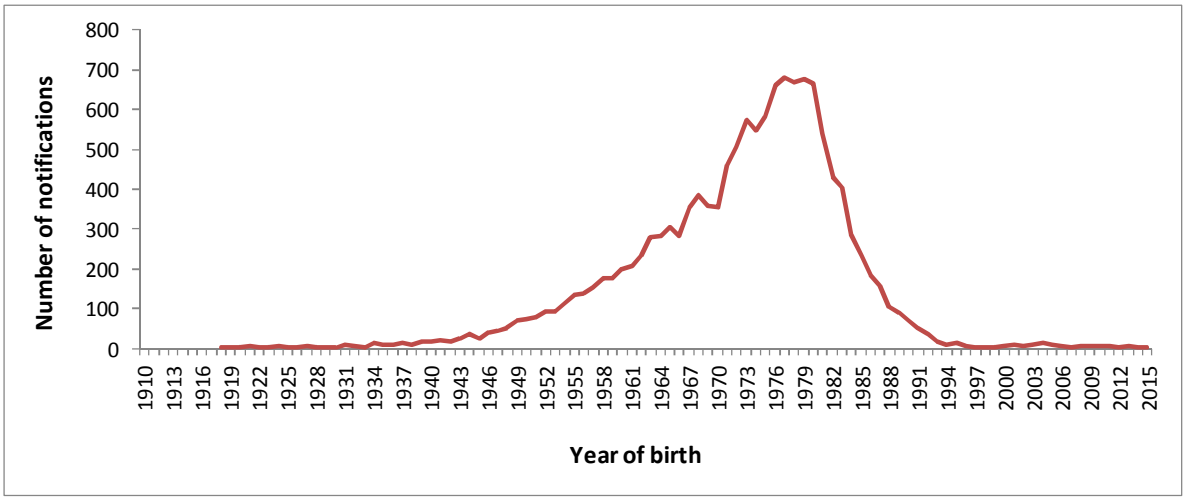

Figure 2. Birth year of diagnosed cases of hepatitis C in CIDR, 2004-2016* (data up to 14th June 2016)

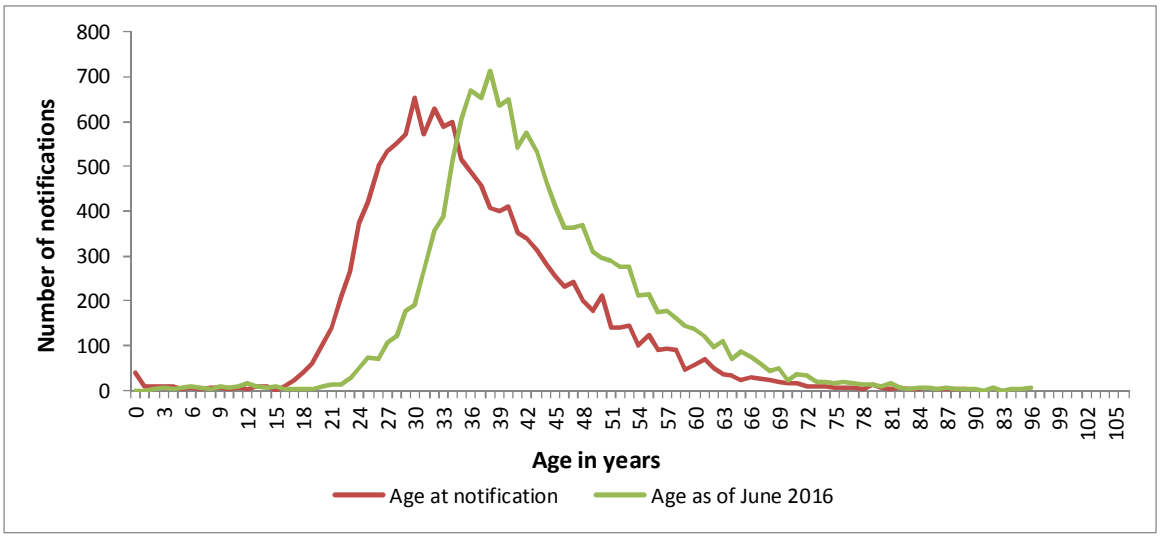

Figure 3. Age distribution of cases of hepatitis C in CIDR, 2004-2016* (data up to 14th June 2016)

Table 1. Birth cohort comparison USA and Ireland (based on notification data in Ireland)

	USA	% chronic HCV (NHANES gen pop data)	Numbers in this age group in US pop	% of US pop	Ireland	Age group (2016)	% cases on CIDR	Numbers in this age group in Irish pop 2011 census	% of Irish pop 2011 census
High incidence period	1970-1990[6,7,8]				1988-2008*				
Birth cohort	**1945-1965**	76.6	84.2 mill	27%	1965-1985	31-51	72.5	1426156	31.1
Alternative wider cohort	1945-1970	87.3	105.1 mill	34%	1960-1985	31-56	81.1	1687181	36.8

*(based on unpublished work on IDU cohort- HPSC/HRB. Personal communication L Thornton)

Burden of hepatitis C infection in Ireland

- **HCV seroprevalence study in Ireland 2016 using residual sera (paper submitted for publication).**[9] A random sample was selected comprising persons ≥18 years with probability proportional to the general population age-sex distribution. The results showed a seroprevalence of anti-HCV of 0.98% (0.73%-1.3%) and a prevalence of chronic infection of 0.57% (0.40%-0.81%). Based on this, it is estimated that 19,606 persons in the adult population in Ireland have chronic HCV infection. The prevalence of chronic infection was significantly higher in males, in specimens from the east of the country, and among persons aged 30-49 years. Adult males born between 1965 and 1984 from the east of the country have the highest rate of chronic HCV infection (males in east aged 40-49 years 5.2% (2.8%-9.3%), males in east aged 30-39 years 3.5% (1.8%-6.9%)). **The estimate obtained is likely to be the minimum prevalence value as the sampling specifically excluded specimens that would be expected to have a higher risk of being HCV positive** (e.g. from drug treatment services, or submitted for HCV testing).

- **Estimates of total number diagnosed and undiagnosed HCV cases in Ireland based on notification data and laboratory data**:

A study was carried out to convert NVRL laboratory information management system (LIMS) specimen-based data into person-based data and estimate prevalence chronic HCV in Ireland at the end of 2009 based on a combination of NVRL diagnostic and HPSC notifications data.[10] It estimated that by 2009 there were 9,913 chronic HCV cases diagnosed and living in Ireland. This does not take account of people with chronic HCV who had not been diagnosed by that time.

Since then, a total of 5787 additional cases have been notified in the CIDR system, a small proportion of which may not be chronic infections. Therefore, a conservative ballpark estimate for diagnosed, chronic living cases in 2016: 14,000-15,000

- If 40% of cases in Ireland remain undiagnosed, the number of chronic cases would be 23,333-25,000 (0.51-0.55% population prevalence of chronic infection)
- If 50% of cases in Ireland remain undiagnosed, the figure would be 28,000-30,000 (0.61-0.65% population prevalence of chronic infection)
- The peak birth years for diagnosed cases of HCV in Ireland: 1960-1985

It is interesting to note that the findings of the seroprevalence study (which includes diagnosed and undiagnosed cases) is in keeping with notification data (which reflect only diagnosed HCV cases) in terms of most affected birth cohort, sex and geographic distribution, and with the estimates from the NVRL study described above in terms of the total HCV infected population size.

If a birth cohort was selected based on the results of the seroprevalence study, i.e. adult males born between 1965 and 1984 in the HSE East region, the size of this population to be screened would be approx. **252,500**. However, this large group would not be homogeneous in terms of its HCV prevalence. Also, a screening programme targeting a birth cohort of males only would be unlikely to be acceptable.

Pilot study of BBV screening in a Dublin emergency department

A pilot study of opt-out blood-borne virus screening was conducted in a large urban emergency department in Dublin in 2014-2015.[11] Over a 45 week period, 8,839 patients (>50% uptake) were tested for HIV, hepatitis B and hepatitis C. Hepatitis C antibody was detected in 447 (5.05%), of which 58 (0.66% of sample) were new diagnoses. 15% had negative PCR on follow-up. The age range for the newly diagnosed cases was 18-69 years (median 29 years) and 47 (81%) were male. The majority (52) were Irish. 37 were injecting drug users and two were nasal drug users. Fourteen had no risk factor identified. The authors plan to carry out further studies examining the seroprevalence rates in both targeted and non-targeted settings in areas of differing demographics, and will follow this with a cost-efficiency study to examine these testing approaches.

Other countries

Canada

A study was carried out to assess the prevalence of HCV and the acceptability and feasibility of birth cohort screening in Calgary, Canada, following on from the US recommendation on birth cohort

screening.[12] The study population was patients undergoing colonoscopy for colorectal cancer screening as this patient population has a high proportion of baby boomers and the patients are already engaged in care. At the time, it had been estimated that 0.8% of the Canadian population were likely to be HCV infected.

The study was carried out in two parts:

(1) An anonymous survey requesting information about demographic characteristics, acceptability of HCV screening by blood or saliva, risk factors for infection, prior HCV testing and prior HCV diagnosis.
(2) Opt-out HCV testing of stored serum specimens on a random sample of patients from 2011-2012.

Of 1012 respondents, 123 (12%) reported having tested previously for HCV, of whom 9 (7.3%) reported a known diagnosis of HCV. This corresponded to an HCV prevalence of 1.0% (95% CI 0.5%-1.9%) among baby boomers. 90% of remaining patients said they would consent to testing, was slightly more acceptable than blood-based. White patients and those with risk factors were more likely to accept HCV screening.

Of the 483 patients tested for HCV antibodies on stored sera, 77% were baby boomers. 0.8% of baby boomers screened were positive for anti-HCV antibodies, 0.5% being chronically infected The cohort was a highly educated group, attending for colorectal screening, and less likely to include high risk groups, homeless, prisoners, socially deprived.

The authors concluded that acceptance of screening for HCV is high among patients undergoing screening for colorectal cancer in this population. “However, the relatively low prevalence of HCV suggests that the cost-effectiveness of birth cohort screening in this population warrants evaluation before the widespread adoption of this approach.”

In a separate study, a state-transition model was developed to assess the cost-effectiveness of alternative screening strategies for patients with chronic HCV in Canada.[13]

This compared one-time screening (with different treatment options, one of which was DAAs) for 25-64 year olds or 45-64 year olds, against no screening. The authors concluded that a selective one-time HCV screening programme for people aged 25-64 or 45-64 years would likely be cost-effective.

The Public Health Agency of Canada is now reviewing its screening guidance for HCV.

The details of the findings of this study are described in the economic evaluation section below and in the appendix.

Switzerland

Bruggmann, on behalf of the Swiss Cohort Study Group, described the birth year distribution in reported hepatitis C cases in Switzerland.[14] The US recommendation on birth cohort testing for HCV was cited in the introduction to this study. A prior study had estimated the anti-HCV prevalence in

Switzerland to be 1.6% (range: 0.8-1.8%). It had also been estimated that around 50% of those affected were not tested or aware of their infection. There was concern that the treatment uptake rates were low and there was a need to improve detection rates.

Hepatitis C has been a notifiable disease in Switzerland since 1988. The Swiss hepatitis C cohort study (SCCS) collects prospective data on adults aged >18 years with confirmed HCV infections through standardised questionnaires, clinical examinations and laboratory investigations since 2000.

The results of notification data were validated by comparing them with SCCS data.

The notification data showed that 61% of diagnosed cases of HCV were born between 1955 and 1974. In the SCCS, 65% were born between 1955 and 1974. By comparison, 30% of the Swiss population were born between 1955 and 1974.

The authors noted that in comparison with the birth year distribution in the USA, the most affected birth year cohorts were on average 10 years younger in Switzerland and suggested that one reason for this discrepancy could be a later peak in intravenous drug use in Switzerland as a major mode of transmission.

A further study by Bruggmann et al, sought to identify which birth cohort would require the least screening in order to diagnose one new viraemic HCV infection.[15] In addition, it compared the direct cost of screening several different birth cohorts. Historical data on the HCV-infected population in Switzerland were obtained from published literature, unpublished data and government reports. A disease progression model was used to age the infected population to 2015.

The findings were as follows:

- Random screening of the general population could identify 1 case per 159 people screened.
- 75% of those with chronic HCV infection born between 1951 and 1985. Screening of this birth cohort could identify 1 case per 99 screened.
- 50% of those with HCV were born 1961-1980. Screening of this birth cohort could identify 1 case per 90 screened.

The authors concluded as follows: “Considering only the direct cost of screening and treatment informing tests, targeted screening by birth cohort is more effective and cost effective than random screening in the general population.” The study did not compare birth cohort screening to risk based screening.

Economic evaluations of birth cohort screening

A number of studies identified in the economic literature review evaluated birth cohort screening. Two systematic reviews were also identified which summarised economic evaluations of birth cohort screening(3, 7)(3, 6)(3, 5)(3, 4)(3, 4)(2, 3)(1, 2).[16,17] Most identified studies were from the USA, with one from Italy and one from Canada. Studies compared birth cohort screening to either no screening or risk based screening in the particular age cohort.

The individual studies are summarised in the appendix.

Coward et al (2016) (3)[6], in a systematic review which summarised the economic evaluations of birth cohort screening, reported that the incremental cost per QALY gained in included studies ranged between £3706 and £45123 (using data from original articles this corresponds to between €7,769 and €64,650[*]). In studies which evaluated different treatment regimes, the addition of DAAs increased the cost per QALY gained. The authors concluded that treatment of choice and cost of treatment can change the conclusion of the model. They also reported that the main source of variation was due to prevalence estimates, and screening and treatment uptake estimates used.

Correti et al, in their systematic review, concluded that studies generally proved the cost effectiveness of screening for specific age cohorts in which the disease prevalence is high and life expectancy sufficiently long.[17]

Coward et al discuss how the cost effectiveness of a programme will depend on the prevalence, acceptability of screening, and uptake of treatment.[16] The economic evaluations to date haven't included the costs of implementation. **It is likely that the implementation plan required to achieve the necessary uptake of screening and treatment in order for a birth cohort programme to be cost effective will be high. The authors conclude that a thorough budget impact plan, including the implementation plan, would be required to assess any such programme.**

Discussion note

The generalisability of birth cohort studies from the US to the Irish population needs to be considered. Of note, the studies compared birth cohort screening to either no screening or risk based screening within the same cohort. If implemented, other screening strategies would likely still be required for those at risk outside of this cohort. Birth cohort screening would be additional to, rather than in place of, other screening strategies. If the budget for screening implementation is limited, prioritising other strategies targeted at those at risk of ongoing transmission may be better. The birth cohort studies also did not analyse the distribution of benefits which may be achieved with birth cohort screening, only the total benefit. Any birth cohort programme would need to consider the health equity impact and also the impact it may have on onward transmission compared to risk based screening or targeting those at risk of onward transmission.

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[*] Inflated to 2014 and converted to Irish euro.

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Studies included in the systematic reviews of the economic literature

McGarry et al (2012) performed a CUA using a Markov model on a hypothetical cohort in the US (8). They compared a risk based screening approach to birth cohort screening of those born between 1946 and 1970. The birth cohort screening approach would last 5 years and then return to risk based screening. A lifetime time horizon was used. A payer's perspective was used and only direct medical costs were considered. Cost and utilities were discounted at 3%. Screening was with ELISA followed by PCR if positive. They assumed eligible patients were treated with Peg-IFN-RBV, with genotype 1 patients receiving DAA combination therapy. It was assumed that over 5 years all eligible persons were screened. Birth cohort screening resulted in an ICER of $37,700 (€37,073[*]) per QALY gained compared to risk based screening. Sensitivity analyses showed that the ICER was sensitive to the reducing the time horizon, treatment rates and treatment efficacy.

McEwan et al (2013) used a Markov model to compare risk based screening to birth cohort testing in the US based on a birth cohort of 1945 to 1965 (9). They assumed a health care payer's perspective and included only direct medical costs. A lifetime horizon was used. Costs and utilities were discounted at 3.5%. Birth cohort screening was found to be cost-effectiveness with an ICER of $28,602 (€26,331*). This assumed 91% of the population is tested, and at least 278,000, 26% of identified population, were treated to generate sufficient cost offsets and QALY gains at a willingness to pay threshold of $50000. Cost-effectiveness was optimised when patients were treated immediately and those with more advanced disease are prioritised.

Rein et al, (2012) used a Markov model to compare a range of screening and treatment strategies in a US population born between 1945 and 1965 (10). They used a societal perspective and lifetime time horizon. Scenarios included no screening, risk based screening and Peg-IFN-RBV treatment; birth cohort screening and Peg-IFN-RBV treatment; and birth cohort screening with DAA treatment for genotype 1. Screening was with a once-off anti-HCV ab. Birth-cohort screening followed by Peg-IFN-RBV resulted in an ICER of US$15700 per QALY gained compared to risk based screening. When birth cohort screening was followed by DAA treatment for genotype one an ICER of $35 700 (€36,304*) per QALY resulted compared to risk based screening and $73 700 (€36,304*) when compared to birth cohort screening with Peg-IFN-RBV. Sensitivity analysis showed the ICER to be most sensitive to sustained viral response of antiviral therapy, the cost of therapy, the discount rate, and the QALY losses assigned to disease states.

Coffin et al (2012) used a Markov model to compare risk based screening, general population (20-69 year olds) screening and birth cohort screening (1945 -1965) (6). A payer's perspective was taken and only direct medical costs considered. A lifetime time horizon and a discount rate of 3% was used. General population screening resulted in an ICER of between $7900 and $49000 (€7,769 and €48,185[*]) depending on uptake and disease progression compared to risk based screening. The birth-cohort scenario which assumed 15% of those born between 1945-1965 were screened had an ICER of $5400 (€5,310*) compared to risk based screening and dominated general population screening scenarios.

Liu et al (2013) undertook CUA using a Markov model. Costs included healthcare costs including out-of-pocket (11). The population included the general population aged between 40 and 74 years. They compared no screening and standard treatment to risk based screening and birth cohort screening with various treatment regimens (standard therapy (Peg-IFN-RBV), IL28B guided triple therapy (Peg-IFN-RBV+PI), and universal triple therapy. One time screening was undertaken at a routine medical visit with an ELISA, followed by two ELISAs, a RIBA, and an RNA test in those initially positive.

[*] Inflated to 2014 and converted to Irish euro.

Birth cohort screening with triple universal triple therapy and IL28B guided triple therapy had ICERS of US$65749 and US$60590 (€64,656 and €59,582[*]) respectively compared to no screening and standard therapy. No screening and IL28B guided triple therapy had an ICER of $50417 (€49,632[*]) compared to no screening and standard therapy. Other scenarios were dominated by the reference scenario of no screening and standard therapy. The age of the target population and disease prevalence were significant on sensitivity analysis. The author's concluded that one time, birth cohort (40-64yrs) screening of asymptomatic adults is likely to be cost effective provided healthcare system has capacity to deliver prompt treatment and appropriate follow-up care.

Rugerri et al (2013) used a CUA to compare no screening and treatment of patients with cirrhosis of HCC to screening of the general population aged 35 years and older in Italy (12). A health service perspective and a lifetime horizon was used. Costs and utilities were discounted at 3.5%. Screening was with Anti-HCV Ab followed by PCR if positive. Treatment was Peg-IFN-RBV. An ICER of was €5,171 (not adjusted) per QALY gained was determined compared to no screening. Results were sensitive to the age of the target population, the prevalence, and the time horizon used.

Wong et al.(2015) undertook a CUA based on a Canadian monoinfected hypothetical cohort (13). They compared no screening to once off general population screening of those aged 25-64, and no screening to once off screening of those aged 45-64. For both age groups various treatment scenarios were used including: Peg-IFN-RBV; simeprevir-based combination therapy (genotype 1), sofosbuvir-based combination therapy (genotype 2 and 3) or Peg-IFN-RBV (other genotypes); and a third scenario where patients with genotype one were treated with ABT-450-based interferon free combination therapy. In the screening arms individuals were offered screening by a primary care physician at a visit for another reason. Screening was by HCV antibody followed by HCV RNA if positive. A payer's perspective was used. Costs and benefits were discounted at 5%.

The ICER for screening of the 45-64 year age cohort ranged betweenCA$34359 and CA$55151 (€23,394 and €37,551[*]; assuming cost year of 2013) compared to no screening. For the 25-64 year age cohort screening followed by treatment with Peg-IFN+RBV had an ICER of $38117; and when followed by treatment with interferon-free DAA for genotype 1 was$34783. The treatment scenario using the interferon based DAAs dominated.

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