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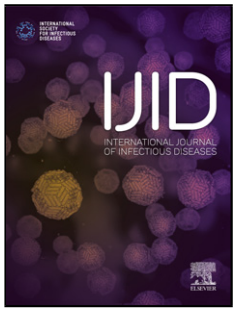


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# HEPCARE EUROPE- A Case study of a Service Innovation Project Aiming at Improving the Elimination of HCV in Vulnerable Populations in Four European Cities.

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## Highlights

- An integrated system of care for HCV is effective to access vulnerable populations
- An integrated system of care greatly improves the cascade of care for HCV including cure
- An integrated system of HCV care is cost effective
- An integrated system of HCV care is replicable in four European countries informing reproducibility and scale-up.

**Objectives**

Hepatitis C Virus (HCV) is an important cause of chronic liver disease. Among at-risk populations, access to diagnosis and treatment is challenging. We describe an integrated model of care, Hepcare Europe, developed to address this challenge.

**Methods**

Using a case-study approach, we describe the cascade of care outcomes at all sites. Costing analyses estimated the cost per person screened and linked to care.

**Results**

A total of 2608 participants were recruited across 218 clinical sites. HCV antibody test results were obtained for 2568(98•5%), 1074(41•8%) were antibody-positive, 687(60•5%) tested positive for HCV-RNA, 650(60•5%) were linked to care and 319(43•5%) started treatment. 196(61•4%) of treatment initiates achieved a Sustained Viral Response (SVR) at dataset closure, 108(33•9%) were still on treatment, 8(2•7%) defaulted from treatment, and 7(2•6%) had a virologic failure or died. The cost per person screened varied from €194 to €635, while cost per person linked to care varied from €364 to €2035.

**Conclusions**

Hepcare enhanced access to HCV treatment and cure, costs were affordable in all settings, offering a framework for scale-up and reproducibility.

**Keywords**

Hepatitis C, Vulnerable populations, people who inject drugs (PWID), integrated HCV care, cascade of care, system of care, HCV elimination

**Background**

The number of people with chronic Hepatitis C Virus (HCV) infection in the European Union/European Economic Area (EU/EEA) region is estimated to be 5.6 million.[1] Chronic HCV infection can remain asymptomatic, leaving people unaware of their status. In the EU, 63·3% of all HCV infections are undiagnosed, with considerable variation between countries. [2] The HCV care cascade has numerous stages from screening to cure. Historically attrition from each stage of the cascade was high, with 5·9% of those testing HCV antibody positive achieving cure pre-DAA availability.[3] In Ireland, our pilot study among the homeless, that was designed based on a systematic review [4] showed that out of 597 patients, 199 were antibody positive, and only two completed HCV treatment demonstrating the need for alternative models of care.[5] Recently,[6] WHO (World Health Organisation) stated that better HCV models of care are needed to retain patients along the care cascade, that an efficient health system must deliver essential HCV treatment services to different populations and settings, reinforce strategic linkages between different health services, ensure quality and engage communities. The HepCare Europe project sought to improve systems of care for vulnerable HCV infected populations, assisting progress towards HCV elimination in line with WHO recommendations[8] and the EU HCV Manifesto.[7] In light of new technological and medical breakthroughs, we endeavoured to improve outcomes at each stage of the care cascade by implementing interventions at four sites London, Bucharest, Seville, Dublin,[8] performing economic analyses to determine whether interventions were value for money.

**Methods**

*Study design*

A service innovation project and a mixed-methods, pre-post intervention study, Hepcare has designed and delivered interventions in Dublin, London, Seville and Bucharest to enhance People Who Inject Drugs (PWID) engagement and retention in the cascade of HCV care. The study started in May 2016 and ended in August 2019 at all sites. We are presenting a case study of this integrated system of care for vulnerable populations.[8] A description of the model of care is shown in Figure 1. The same

model was applied at each site. Each hospital targeted community organisations in their catchment area for outreach. Community organisations therefore varied from city to city. PWID were targeted for intensified HCV screenings (HEPCHECK),[8,9] linked to care (HEPLINK)[10] and supported to remain engaged with the cascade of care using peer support (HEPFRIEND).[11] HEPED developed and delivered educational interventions to prepare affected communities for HCV testing, assessment and treatment and to prepare healthcare providers to act as partners in a shared care primary/secondary partnership for treatment of HCV.[11] HEPCOST evaluated the cost of the various Hepcare interventions in the different settings.

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Quantitative data on cascade of care and costing of the different initiatives were collected. In Dublin, London, and Bucharest, intervention costs were collected from healthcare providers; costs were not available from the Seville intervention due to staffing limitations.[12] Costing analyses were undertaken using top-down and ingredients-based approaches depending on information available at each site. The most up-to-date costs for all resources used were collected and all retrospective costs were inflated to 2018 Euros using the Consumer Price Index for health. Country-specific prices were converted to a standard price index by adjusting for differences in GDP using the purchasing power parity value for 2018.[13] Financial and economic costs were collected and classified as capital (one-off costs) or recurrent (staff and test costs). Data collected for project activities included intervention set-up, non-research intervention activities and staff usage. Expenditure costs were recorded. Research related costs were excluded. Costs for capital items were annualized over a 5-year period with computer equipment costs annualized over 2 years. The outcomes of cost per patient screened, diagnosed with infection, or linked to care was estimated by dividing the total cost by the number of individuals in each category. The cost per person treated was not estimated because treatment rates were affected by differences in regulatory barriers across settings restricting some patients from obtaining treatment.

*Settings and Recruitment*

The study was conducted across four European cities: Dublin, Cork( Ireland), London( UK), Seville( Spain), and Bucharest( Romania); and targeted high-risk populations. Recruitment was carried out by

each city hospital in surrounding community settings through outreach in community addiction, prison, homeless services and GP practices prescribing methadone. .[14]

**Results**

*Networks created*

The types and numbers of services who participated to the Hepcare outreach initiative varied from city to city. Table 1 presents types of clinical service that participated in the project, with outreach being undertaken across 218 services in four European cities, including homeless services, addiction services and prisons. More community sites were reached in London due to the use of a mobile health unit. Seville mostly targeted drug treatment centres and NGOs, whereas Dublin mainly targeted a prison and GP practices. Bucharest targeted night shelters and community organisations. Across the European sites, homeless services represent 49·1% and drug addiction centres represent 34·9% of the services reached.

*Type of testing*

The rapid oral swab test was the most popular antibody testing method used (50·1%, n=1291). In Ireland phlebotomy was used as a first testing option among prisoners due to an ethical ruling.

*Cascade of Care*

The cascade of care results and their breakdown by site are shown in Table 2. Overall, 2608 participants were recruited across the four European countries with 2568(98•5%) participants receiving an HCV antibody test. Of these, 1074(41•8%) had an HCV antibody positive result and 687 (60•5%) were HCV-RNA positive. Overall, 650(64•0%) were then linked to care and 319(43•5%) started treatment. At dataset closure (31 July 2019), 196(61•4%) of participants that started treatment had achieved SVR, 108(33•9%) were still on treatment, and 12(4%) had other treatment outcomes. The rates of HCV antibody positive participants linked to care in each country varied depending on the system used. For some sites RNA testing was offered in the community, whereas other sites could only undertake RNA testing after linkage to care in hospitals. Ireland had the highest proportion of participants linked to care

that subsequently started treatment n=104 (64.2%). The effectiveness of HCV DAA treatment is verified in our study with 196(96•5%) individuals achieving SVR of the 203 that completed treatment however Romania had a higher percentage of virological failures with 10%.

*Economic Analysis*

Table 3 presents the total costs of the main HepCare interventions in Dublin, Bucharest and London. These costs do not include costs of treatment or treatment workup. The London outreach intervention was most expensive (£97,472 or €112,093) with active case finding in a mobile van. Next was the prison mass-screening intervention in Dublin (€81,505), the intervention in OST GP practises in Dublin (€64,806) and multiple interventions in Bucharest (€56,647). The main cost components for Dublin were overheads, primarily due to the inclusion of management staff time during implementation. In contrast, salary costs for undertaking screening was the most expensive component in London (58% of total costs), while in Bucharest, the highest costs were for training (23%) and peer support (23%). The high London salary cost for screening is related to having a HCV specialist nurse, peer and driver for the mobile intervention. In contrast, salary costs for screening in Bucharest were less costly (7%) compared to other settings.

Table 4 compares the costs per outcome for each setting. These outcomes differ to what is presented in Table 2 because the costing analysis only evaluated two interventions in Dublin and one in London. Additionally, the London intervention was costed over one financial year (2017/18) and so patient outcomes were taken from that period. The cost per person screened varies 3-times across settings after adjustment to 2018 Irish Euros, with the two Dublin interventions having the lowest (prison screening €194) and highest (OST screening €635) unit cost. The high cost from screening in the OST clinic in Dublin is due to small numbers of patients screened. Unit costs increase 2-10 times for the cost per person linked to care, reflecting that only a proportion of people tested are infected, which varies by setting, and not all those infected are linked to care. Although the prison intervention in Dublin has the lowest unit cost for screening, it then has the highest unit cost per person diagnosed due to the low proportion of HCV infected patients (12% were RNA+) amongst those screened. Cost per person linked

to care for the London outreach intervention is higher than cost per person diagnosed due to the cost of using peer support to facilitate patient attendance to secondary care.

**Discussion**

HepCare accessed a high number of vulnerable patients in all four cities through joining up and improving services. Although it was thought that oral swabs were the best testing method for the project, in practice, a key part of the system's success relied on flexibility in the testing methods to engage community partners.

Despite significant successes, the HepCare system's effectiveness was limited because of social, regulatory, medical reasons and capacity to access certain populations. Bucharest faced medical and regulatory barriers which meant they could only treat 24(33•8%) of their 71 diagnosed HCV RNA+ participants. Until 2018, DAA treatment was only available for advanced liver fibrosis (Metavir F3 and F4 score) in Romania, so most patients from Bucharest with lower fibrosis stages, were not eligible for reimbursed investigations and treatment by the national insurance system. Also some patients may have not been treated with suitable DAA regimens because genotype testing was unavailable for PWID in Bucharest, contributing to the 2 reported virologic failures (10% of HepCare Bucharest). Most importantly, the Romanian National Insurance scheme requires an individual to have an identity card, a health-card and insurance before accessing HCV diagnostics and treatment. This presented a significant barrier because 143 HCV antibody positive prisoners were neither tested for HCV-RNA nor treated because they did not fulfil these criteria. In Dublin, the limited healthcare budget and high cost of DAA regimens restricted availability of treatment, from July 2017 to February 2018 with a freeze of new treatments imposed by the government. This significantly disrupted the HepCare 'cascade of care' among targeted vulnerable populations where timeliness is key to keeping patients engaged in care. Hepcare Seville could not access two key populations, prisoners and immigrants. In London some key populations such as the Roma, traveller communities and sex workers were hard to reach with existing

peers. Finally, our costing analysis suggests affordability of the interventions, although a comparison of the costs per outcome reached at each point in the care cascade reveals wide variations between settings due to differences in the HCV prevalence, availability of confirmatory testing and barriers to linkage to care.

Hepatitis C care has undergone tremendous changes due to technological advances including non-invasive rapid tests (e.g. Oraquick® and fibroscan technology)[15],[16] [17] and DAA treatments.[18] This has enabled new possibilities and the rapid expansion of systems of care for HCV. The Hepatitis C Assessment and Testing (HepCAT) project in New York, a prospective cross-sectional project conducted in three primary care clinics in low economic activity areas,[19] increased both numbers screened and diagnosed. It increased HCV diagnosis and linkage to care, but did not report subjects achieving SVR. Conversely, HepCATT (Hepatitic C Awareness Through to Treatment), UK, had two branches recruiting from primary care and drug treatment services.[20] [21] The HepCATT drug treatment service study was a nurse-led intervention to increase case-finding and linkage to care, utilising 'buddies' and peers. Compared with baseline and control districts, there was strong evidence that HCV testing and engagement with HCV therapy increased substantially. An economic evaluation of the intervention showed comparable costs for screening and engagement as found for HepCare, with costs per person screened (reflex testing of dried blood spots) ranging from £106-£207 (management costs not included).[22] Other work in Tayside (Scotland)[23] has created a new pathway that allows pharmacist to undertake HCV testing, prescribe medicine and observe patients taking medication.[24] This Scottish model was also applied in Opioid Substitution Therapy (OST) clinics and Needle and Syringe Exchange Programmes (NSP). This model is at the forefront of new systems of care that devolve HCV care to the community. It is not yet easily adaptable to other settings because pharmacists have no legal authority to undertake such services. Compared to results prior to HepCare[10], [14] the system improved outcomes. Costs of the HepCare interventions compare favourably with the range of costs per case detected (£245-3107) from a systematic review of economic evaluations of screening for HCV[25] and the costs from more recent intervention evaluations (£100 to £318 per person screened).[26] [27] [28]

Devolution of HCV care to the community effectively reaches vulnerable populations, but cannot supply specialty care needed for complex cases including cirrhotics. HepCare is the blueprint model that can be used across a range of health-care systems and community settings for micro-elimination of HCV. Focus on one disease may be a weakness, although those engaged in HepCare may be more likely to access other health services in the future. Projects such as INTEGRATE[29] are focussing on integrating various diseases.

Strengths of the costing analysis include the collection of empirical cost data from numerous interventions in three countries, aiding generalisability of findings to other European settings. However, limitations include being unable to undertake a costing analysis in Spain, which used a nurse-led model similar to London, but no mobile unit. The costing methods used in different countries were also slightly different in order to make the best use of available information. Whilst this means the results may be less comparable, it reflects the nature of the populations being screened and the different approaches needed in each. The variation in costs across settings is due to differences in the interventions undertaken, as well as local differences affecting the investment needed in staff time versus materials. The costing analyses did not include the cost of treatment or related visits and diagnostics because the focus was on the costs of screening and linkage to care, and treatment rates were affected by local regulatory restrictions. At the time, all treatments (except in the Dublin prison) were done in hospitals, meaning that the treatment costs should be similar in each setting regardless of the screening and linkage to care intervention. This will change as treatment moves to the community. We also did not undertake a full cost-effectiveness analysis because this is the focus of separate analyses – here we compared the differences in unit costs of the interventions across settings, which is useful information for other settings planning the resource needs for undertaking similar interventions. Finally, these were pilot interventions in which we were unable to assess the resources needed to scale them up to the wider population. As interventions scale-up, there will be cost savings from reduced managerial or training costs. In addition, over time prevalence is likely to change, with high rates of treatment leading to reduced prevalence and therefore the cost per diagnosis may increase unless screening becomes more

targeted. In high incidence populations such as PWID, this change is likely to be slower due to re-infections.

HepCare has impacted on policy and practice. In Dublin, the project developed an advocacy document (HEPMAP) disseminated to the Irish Health Service Executive. In Bucharest recommendations were sent to the National Infectious Diseases Committee and Director of the National Programmes in the Ministry of Health. HepCare successfully changed HCV treatment policies toward at–risk populations by promoting the recent removal of disease-based and laboratory restrictions permitting the treatment of all patients (September 2018). In Seville, the HepCare model was replicated at other tertiary care centres in 8 Andalusian provinces. Outside Andalusia, centres in Valencia and Galicia are planning to implement the model. In London, the HepCare mobile outreach model of care has inspired other services including the Hepatitis C Trust who is launching a similar mobile screening service with the NHS in southern England to access hard-to-reach patients directly based on the HepCare model. St Mungo's, the largest provider of homeless accommodation in London, now has regular screening programmes due to the partnership.

The cost analysis has revealed that numerous different interventions can be affordable across Europe. One important lesson is that the yield of testing is a big indicator of costs, varying unexpectedly across testing settings. In Bucharest, high HCV prevalence was expected in homeless shelters but this was not the case. Perhaps pilot screening measures in proposed high-risk groups could be used to make more informed judgements of the best way to target initiatives. Otherwise, staff costs varied and were large in some settings. Interventions could be made more efficient through optimising these costs. Incorporating screening into existing services will be more efficient than setting up whole new interventions.

**Conclusion**

This first multi-city study offers a framework for scale-up and reproducibility for achieving HCV elimination goals. However, vulnerable populations have numerous health conditions, highlighting the importance of integrating multiple health needs as initiatives are expanded. To achieve HCV elimination and other targets of the Sustainable Development Goals (SDG) 2030 agenda, it is imperative to reach vulnerable populations not accessing care and leave no one behind.

**Transparency declaration**

JL has received non-restricted grants from Gilead, Abbvie and MSD for Hepatitis C related educational and research activities. JL has received honorariums for advisory board meetings on HIV and HCV, organised by Gilead, Abbvie, Glaxo Smith Kline, Viiv, and Merck. WC has been a principal investigator on research projects funded by the Health Research Board of Ireland, the European Commission Third Health Program and Ireland's Health Services Executive. WC has also been a co-investigator on projects funded by Gilead and Abbvie. JM has served as an investigator in clinical trials supported by Bristol Myers-Squibb, Gilead and MSD. JM has also served as a paid lecturer for Gilead, Bristol-Myers-Squibb, and MSD, and has received consultancy fees from Bristol Myers-Squibb, Gilead and MSD. JM has received a grant from the Servicio Andaluz de Salud de la Junta de Andalucia. CO has served as a paid speaker for Janssen, BMS and Abbvie; has served as an advisory board member for Teva, ViiV, and Gilead, and as a principal investigator on clinical trials supported by ViiV, and as a co-investigator on clinical trials supported by Abbvie and Tibot. PV has received unrestricted research grants off Gilead and honorarium from Gilead and Abbvie.

**Authors' contributions**

Gordana Avramovic- Review of pilot project, Study design, Figures, Data Collection, Data analysis, Data interpretation, manuscript writing. Maeve Reilly -Data Analysis, manuscript writing. Walter Cullen- Literature search, review of pilot project, study design, data collection, data analysis, manuscript review. Juan Macías- Study design, data collection, data analysis, data interpretation, manuscript review. Geoff McCombe, Literature search, data collection, manuscript review. Tina McHugh- Data collection, data analysis, manuscript review. Cristiana Oprea- Study design, Data

collection, data analysis,data interpretation, manuscript review. Alistair Story- Study design, Data collection, data analysis, data interpretation, manuscript review. Julian Surey- Study design, Data collection, data analysis, data interpretation, manuscript review. Sandra Bivegete- Data collection, data analysis, manuscript writing. Peter Vickerman- Study design, data collection, data analysis, data interpretation, manuscript writing. Josephine Walker- Data collection, data analysis, manuscript writing. Zoe Ward- Data collection, figures, data analysis, manuscript writing. John S Lambert- Literature review, pilot project review, study design, Data Analysis, Data interpretation, manuscript review. All authors have approved the final version for publication and are accountable for all aspects of the work.

**Ethics Committee Approval**

Ethical approval was granted by the Institutional Review Boards in each of the sites namely: Mater Misericordiae University Hospital (Dublin, Ireland); North-West Haydock Research Ethics Committee (London, UK); Hospital Universiario de Valme (Seville, Spain); and Victor Babes Clinical Hospital for Infectious and Tropical Diseases (Bucharest, Romania). Governance and oversight for the study were provided through the overall governance structure of the HepCare Europe Project.

**Data**

Existing ethical approvals allow for the publication of aggregated anonymised data to be reported.

**Declaration of interests**

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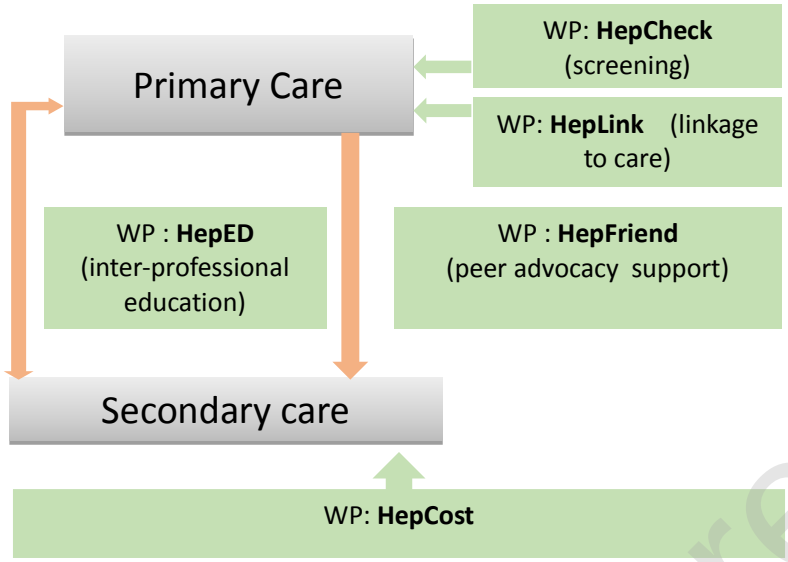
**Role of the funding source**

This research was co-funded by the Health Programme of the European Union and Ireland's Health Service Executive. Funders were not involved in implementation or analysis, interpretation or writing.

**Figure 1: The HepCare Europe System**



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