Health Protection Scotland

The Scottish Government

Proposal for Consideration by the Scottish Government

Scotland's Hepatitis C Action Plan: Achievements of the First Decade and Proposals for a Scottish Government Strategy (2019) for the Elimination of both Infection and Disease

Taking Advantage of Outstanding New Therapies

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On Behalf of Scotland's Hepatitis C Stakeholders (See Acknowledgements)

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1 Background

Ten years have elapsed since the Scottish Government launched fully a Hepatitis C Action Plan (1, 2) to address the country's hepatitis C problem; in 2008, 38,000 (0.7%) of the population were estimated to be chronically infected and over 90% had injected drugs.

The overarching aim of the plan was to reduce the anticipated burden of liver disease due to hepatitis C by i) improving services to prevent transmission of infection, particularly among people who inject drugs (PWID), ii) identifying those infected and iii) ensuring that diagnosed people needing therapy get it. This ongoing plan is underpinned by significant funding (around £100 million, additional to the general NHS funding pot, had been invested in services between 2008 and 2015), and is comprised of numerous initiatives ranging from the education of children to the rapid scale-up of antiviral therapy. Adopting a performance management approach and supported by a web of accountable national and local multi-disciplinary networks responsible for the planning, development and delivery of services, the Scottish plan has been cited as an example of best practice by the WHO (3), the World Hepatitis Alliance (4), the European Commission (5) and the United Nations Drug Policy Unit (6).

Action Plan recognition was also manifested by the World Health Organization and World Hepatitis Alliance staging their inaugural World Hepatitis Summit in Glasgow in September 2015.The Summit's Glasgow Declaration on Hepatitis declared WHO's plan to eliminate Hepatitis B and C by 2030 - a declaration made in advance of the formal announcement at the World Health Assembly, Geneva, in May 2016.In the Scottish Government's NHS 70 timeline celebrating the 70th anniversary of the NHS in Scotland, the Action Plan is cited as one of a select list of achievements(7).

This report reflects on how the Action Plan was established and what it has achieved a decade after its launch. It also reflects on changing Government policy over this time and sets out future policy to achieve the elimination of both infection and disease.

2 Scottish Government responds to the Challenge of Hepatitis C: Timeline

2006: Scotland's Hepatitis C Action Plan Phase I: The Scottish Government makes a commitment to the hepatitis C challenge and requests a fully costed needs assessment.

2007: Scottish Intercollegiate Guideline Network guidelines on the management of Hepatitis C published (revised 2013).

2008: Scotland's Hepatitis C Action Plan Phase II: Serious investment (approximately £15,000,000 per year of additional dedicated funding) for education, awareness raising, prevention, diagnosis and treatment/care services, and for coordination, monitoring and research, is made available.

: The introduction of hepatitis C treatment targets

2008: The Scottish Government announces the Penrose Inquiry into the transmission of hepatitis C and HIV from blood and blood products to NHS patients in Scotland.

2011: The incorporation of the Scottish Hepatitis C Action Plan into a Sexual Health and Blood Borne Virus Framework.

2014: The Scottish Medicines Consortium approves the introduction of the new highly effective direct Acting Antiviral Agents for hepatitis C in Scotland; these are deemed to be highly cost effective.

2015: The Scottish Government supports Glasgow hosting the World Health Organization's inaugural World Hepatitis Summit. At the summit, the Glasgow declaration on hepatitis is made; it calls on governments in all jurisdictions to commit to the elimination of both hepatitis B and C.

2015: The Scottish Government approves Scotland's Hepatitis C Treatment and Therapies Group Report, recommending i) the elimination of hepatitis C as a serious public health concern and ii) the prioritisation of hepatitis C treatment (in terms of timing only) for those with moderate to severe liver disease.

: The introduction of a hepatitis C disease target

2015: The publication of the Penrose Inquiry Report; its single recommendation concerns the offering of hepatitis C testing to people at risk of infection as result of blood transfusion or blood factor treatment in Scotland.

2016: The publication of the Penrose Inquiry Recommendation Report; a short life working group advises the Scottish Government on the implementation of the Penrose Inquiry recommendation. A targeted awareness campaign follows.

2018: The Scottish Government approves Scotland's Hepatitis C Treatment and Therapies Group recommendation to lift the prioritisation of hepatitis C treatment restriction.

2018: The short life working group on Hepatitis C Case Finding and Access to Care publishes its recommendations.

2019: The Scottish Government launches its Hepatitis C Elimination Strategy.

3 Executive Summary: The Scottish Government's (2019) Hepatitis C Elimination Strategy

Context

Scotland's Hepatitis C Action Plan, initiated during 2006-8, has had an enormous impact on tackling one of Scotland's major public health problems and has laid the foundations for the next equally ambitious phase of the Plan:

Achievements include:

Between 2006 and 2018:

- A 45% reduction in the number of people living with chronic hepatitis C from an estimated 38,000 to 21000.
- A 55% reduction in the number of people unaware of their infection from 23,500 to 10500.
- Approximately 16,000 treated of whom an estimated 12,800 (80%) have cleared their virus.

In the Context of the Era of the Direct Acting Antiviral Therapies, available since 2014:

- New presentations of hepatitis C related decompensated cirrhosis (liver failure) declining 67% from a peak of 141 in 2013 to 47 in 2018.
- New presentations of hepatitis C related hepatocellular carcinoma declining 69% from a peak of 58 in 2016 to 18 in 2018.
- Hepatitis C related deaths declining 49% from a peak of 67 in 2015 to 34 in 2018.

The Following Strategy is Proposed

Vision

The elimination of hepatitis C infection and hepatitis C related severe disease and death as a major public health concern by 2024 at the latest.

Definition of Elimination:

Hepatitis C Infection

5,000 or less chronically infected people- i.e: no greater than 1 in 1,000 people of Scotland.

Hepatitis C-related Liver Failure/Liver Cancer/Death

For each outcome, less than 10 people with chronic HCV presenting per year.

Compliance with WHO Elimination Targets

Targets, set by WHO in 2016, for the elimination of Hepatitis C to be achieved by 2030, will be met by the dates as above.

Why

A more rapid approach to elimination will secure undoubted humanitarian benefits with less people experiencing mild, moderate and severe ill-health associated with, and less people dying from, hepatitis C-related disease.

Additionally, it is estimated that the overall costs associated with hepatitis C to the NHS are less if the time when elimination is reached is earlier rather than later.

How

NHS Boards, together with local authorities and third sector organisations, and supported by Health Protection Scotland, should:

- Treat a minimum of 2,500 people during 2019-20 and 3,000 each year thereafter; it is predicted that this strategy will achieve elimination by 2024.
- Guided by the recommendations made by the SLWG on Hepatitis C Case Finding and Access to Care,intensify efforts to identify those people undiagnosed and to re-engage diagnosed people not in contact with hepatitis C services. An eclectic model of hepatitis C care –i.e. the provision of services in both hospital and community settings, tailored to the needs of the patient--should be adopted.
- Ensure that people who inject drugs have access to and take up i) optimal harm reduction services and ii) if deemed clinically ready, antiviral therapy to prevent the onward transmission of infection.

Facilitated by

- A mature web of national and local multi-disciplinary and uni-disciplinary networks established during the early years of the Action Plan.
- Government, public health, clinical and third sector leaders who have achieved outstanding outcomes to date.
- A world renowned service infrastructure ideally placed to take advantage of highly effective, safe, easy to administer and increasingly less expensive therapies.
- Highly sophisticated information generating initiatives to monitor key outcomes.;this programme will need to be enhanced, incorporating general population prevalence studies, to ascertain with reasonable precision the performance of the strategy.
- A programme of research to evaluate the effectiveness of interventions designed to prevent both infection and HCV related disease.
- An Elimination Strategy Implementation Group comprised of experts from a wide range of disciplines.
- An Elimination Strategy project management team.

4 Hepatitis C Action Plan: Establishment

The Evidence Base

Several factors were critical in securing the Plan. High quality information to convince key decision makers of the imperative need for action was required and three main areas of knowledge were drawn on: i) robust evidence, generated over many years through sophisticated monitoring systems, indicating the extent of the problem not just in terms of numbers infected, diagnosed and treated but also numbers presenting with end-stage

disease and dying (8-15), ii) availability of affordable and cost-effective antiviral therapy delivering viral clearance in 40-80% of infected persons, depending on genotype (16) and, iii) compelling modelling work demonstrating the potential beneficial impact of scaling-up therapy on the trajectories of serious disease outcomes and, even more convincingly, the cost of not acting (17). Much of this evidence and its application, while presented in a context specific to Scotland, is highly relevant to HCV infected populations elsewhere.

Hepatitis C Champions and a Coalition of Stakeholders

The principal initiative in creating the environment for the gestation of the Action Plan, was the establishment of a coalition of stakeholders; public health, clinical, and, critically, patient representative leaders, who agreed a consensus approach to deliver the evidence demonstrating the need for action. Building the coalition was dependent on the leadership of a relatively small number of champions who sought to engage colleagues within and across disciplines and raise awareness with civil servants and politicians. The importance of such a multidisciplinary approach cannot be over-emphasised – not just collaboration across traditional medical specialities but across a wide range of health care specialists and providers (including non-statutory ones) involved in all aspects of the care of individuals affected by hepatitis C. Many of those infected are on the margins of society and have difficulty following standard pathways of healthcare provision. Accordingly, it was appreciated that the full benefits of an Action Plan approach would only be realised at the population level by being inclusive of all those affected.

The Role of Government

For the Action Plan to be implemented in Scotland, Government leadership and investment was essential; whatever the healthcare arrangements in other countries, the experience indicates that the role of a national body with fiscal and governance responsibility is critical. The Scottish Government – drawing on the experience of emerging HIV disease two decades before – appreciated the need to provide a “helping hand” to health boards responsible for the delivery of local health care when faced with new, immensely challenging, public health issues.

Other influences on the Government’s decision to implement an Action Plan were time and circumstance specific. In Scotland, crucial favourable socio-political factors included a hepatitis C problem larger than that elsewhere in northern Europe and a devolved Government (devolution occurred in 1999) which encouraged consultation, was already sympathetic to the cause having promised an Inquiry into the HIV/HCV contamination of donated blood and blood products (18) and had and still has, as a flagship mission, the reduction in health inequalities.

In resource-rich countries, there is unlikely to be a condition more associated with deprivation than hepatitis C! The deprivation/HCV connection in Scotland (19) stems from the fusion of injecting drug use – detonated by new sources or heroin from Iran, Afghanistan and Pakistan during the late 1970s/early 1980s – with markets of young vulnerable people, particularly males, who were unemployed in the post heavy-industry era. Efforts in other countries to replicate the Action Plan should identify how action on HCV can align with political agendas and offer opportunities to achieve wider political aspirations and targets.

5 Hepatitis C Action Plan: Achievements

5.1 Introduction

In addition to being a model of good practice for other countries to consider adopting, the performance of the Action Plan has been gauged through the interrogation of Government approved outcome indicator data associated with the following areas: prevention of infection, diagnosis and access to specialist care, treatment and burden of infection/disease.

Service development, however, was underpinned by sophisticated coordination and monitoring systems, newly created or further developed as part of the Plan.

Coordination and Monitoring Achievements

- A nationally and locally co-ordinated, multi-disciplinary and multi-agency approach, covering all geographical areas, settings and spheres of service need (prevention, diagnosis, treatment and care), and underpinned by serious investment, project management expertise and a robust accountability framework, can achieve considerable service development and health improvement success in a relatively short time-frame (2).

- The establishment of accountable and inter-linked local and national networks are vital for optimal service planning and development; the engine room of this network of networks is the health board Managed Care Network – a multi-disciplinary and multi-agency arrangement responsible for planning, developing, implementing and reporting on local services (2, 20). Local Networks are linked to National ones and these report into an Executive Group of NHS Board Leads who are accountable to the Scottish Government. The Chairs of National Networks, for Viral Hepatitis Clinical Leads, the Bloodborne Virus Prevention Leads and the Bloodborne Virus Coordinators, also directly advise the Minister for Public Health.

- The establishment and further development of an Action Plan monitoring, evaluation and research initiative, with the hub at Health Protection Scotland and Glasgow Caledonian University and spokes linking into NHS Boards and other Universities; this arrangement has been vital in ensuring that investment and interventions are applied appropriately, effectively and efficiently. Of particular importance are national clinical and laboratory diagnosis databases, holding information on numbers of people with hepatitis C diagnosed, treated and achieving a sustained viral response (SVR). Such outcome indicator data, now publicly accessible, allow health boards to observe and compare progress made, particularly in the context of treatment initiation targets set by the Government. Additionally, a national survey of Hepatitis C infection and behaviours among People Who Inject Drugs is undertaken every two to three years (see below) (21).

- The initiative as above has further developed and refined record linkage techniques to identify numbers of hepatitis C-infected people experiencing end-stage disease and death outcomes; in the context of the highly effective Interferon-free treatment era, such hepatitis C-related end points—arguably the most important outcome indicators of all-- should be avoidable in the great majority of instances (11-13).

- The generation of all such Action Plan outcome indicator data has been overseen by a Scottish Government led National Monitoring, Assurance and Research Group and the data are held on Scotland's Sexual Health and Bloodborne Virus Framework data portal, accessible to the general public.

Research

Additionally, the Plan afforded a unique opportunity to undertake evaluative research, generating knowledge which is transferable to other countries, particularly ones with similar hepatitis C characteristics. Research findings are listed at the end of each of the four sections as indicated above .These findings, while of importance to an international audience, were germane to shaping both Scottish Government policy and service delivery over the lifespan of the Action Plan. Further details can be found in Hutchinson et al 2015 (50).

5.2 Prevention of Infection (21, 50, 51, 52)

Over the last 10-20 years, it is estimated that between 500 and 1500 people in Scotland have been infected with hepatitis C annually. Nearly all, i.e: 98-99%, acquired the infection through drug injecting behaviours; only the occasional transmission in a non-PWID has been observed and these, invariably, involve either HIV infected men who have sex with men or patients and staff in healthcare settings.

Impact of the Action Plan on Transmission of Infection among PWID

The impact of the Action Plan on the transmission of hepatitis C among PWID has been limited. Prior to the Plan, Scotland's harm reduction services - needle and syringe and opiate substitution therapy provision – were among the best of those anywhere and, during the 1990's and 2000's, the prevalence of infection among PWID declined from around 80% to 60%; harm reduction had reduced but not controlled the incidence of infection among this population. The Action Plan involved a further bolus of investment, directed mainly at providing PWID with other sterile injecting-related paraphernalia – mainly spoons, filters and water—used for the preparation of heroin.

Further, the Plan had spawned a national survey of blood borne viruses and behaviours among 2000-3000 PWID, to be conducted every two to three years (54). Incidence of infection is gauged by monitoring the prevalence of HCV antibody among recent initiates to injecting drug use and by monitoring for hepatitis C virus (PCR RNA) among PWID testing negative for HCV antibody. Over an 11 year period between 2008 and 2018, no sustained reduction in the incidence of infection among active PWID in Scotland was observed (Figure 1); the rate remains around 10-15 per 100 person years of injecting. It is possible that the benefits of scaling up injection equipment provision and opiate substitute therapy have been offset by the disbeneficial effects of changes in drug taking behaviours, particularly in central Scotland. Here, PWID have moved from predominantly heroin injecting to a more evenly balanced mixture of heroin and stimulant (e.g: cocaine) injecting with the resulting increase in injecting frequency.

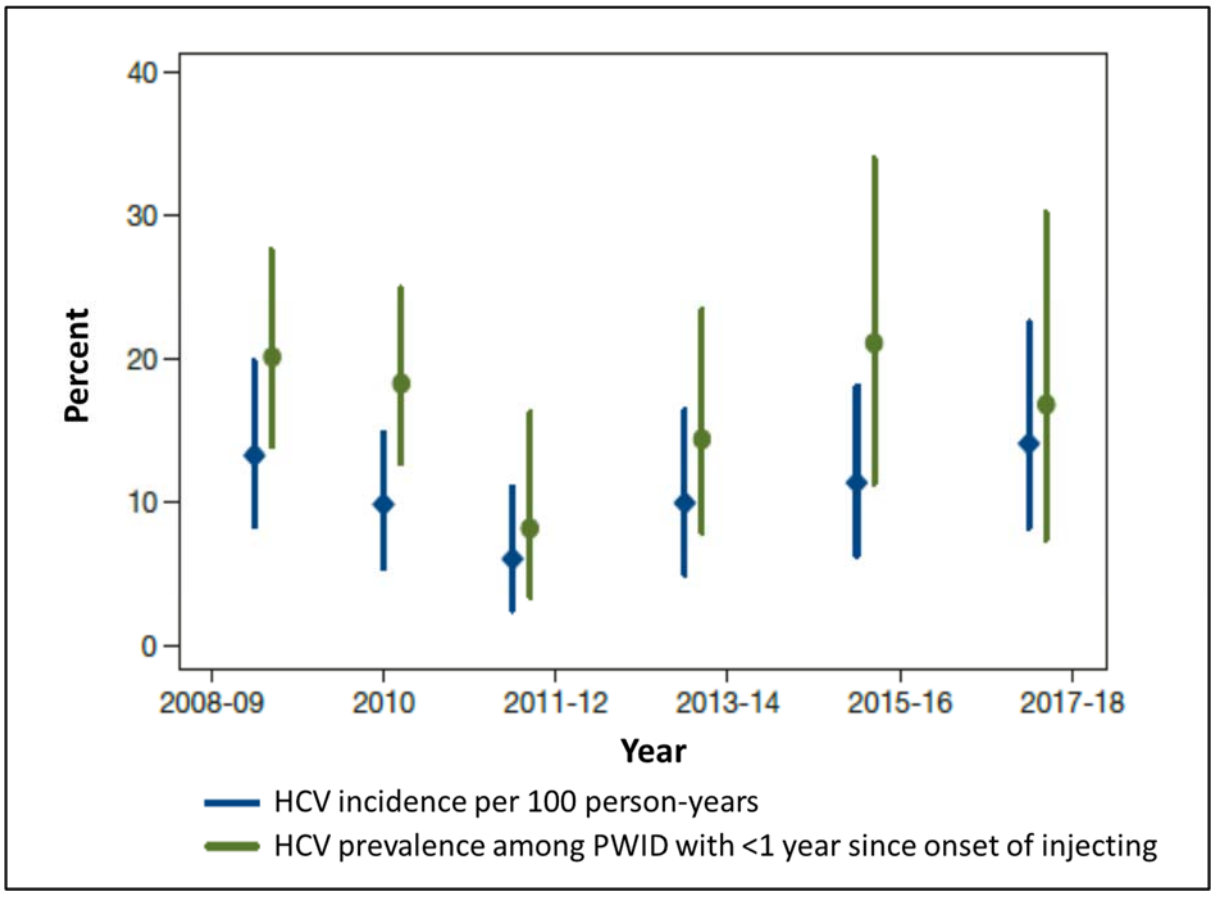

Figure1: Indicators of the Rate of New HCV Infection among PWID in Scotland: 2008-2018 (Ref 54)

Treatment to Prevent Hepatitis C Transmission

Mathematical modelling work has shown that if sufficient numbers of active PWID, infected with hepatitis C, are treated with effective antiviral therapy, there is likely to be a beneficial impact on the incidence of hepatitis C among PWID – i.e. the concept of treatment to prevent onward transmission of infection – as long as harm reduction services are functioning optimally (27, 34). Studies, currently being under taken in the UK (particularly Dundee, see case study below) and Australia will shed light on the potential impact of this intervention in real world situations.

Conclusion

While the incidence of infection amongst active PWID in Scotland remains frustratingly stable, it is likely that the annual number of PWID, newly infected with hepatitis C, is in decline – due to a possible reduction, over the last decade, in the incidence and prevalence of injecting drug use in Scotland, possibly due, in part, to a rise in the number of people taking OST. Ten years ago the number of active PWID in Scotland was estimated to be 16,000; work to estimate the latest prevalence is currently being undertaken.

Drive to Eliminate Hepatitis C in Dundee/NHS Tayside: Case Study

The goal of HCV elimination in places where injecting drug use is the principal risk factor for hepatitis C is theoretically possible but needs to be demonstrated in the real world. Modelling work revealed that HCV treatment is likely to constitute a critical component of the HCV prevention toolbox for PWID - a finding which led to the concept of "HCV treatment as prevention". In Tayside it has been shown that it is possible to successfully deliver therapy to this vulnerable group of individuals (61).

As part of an NIHR funded study (62), NHS Tayside, in association with Glasgow Caledonian University, University of Bristol and other partners, aims to evaluate this concept by rapidly scaling up HCV treatment over three years to reduce chronic HCV prevalence among PWID by two-thirds from 30% to less than 10%. Dundee/NHS Tayside is the study site and certain other areas in Scotland and the rest of the UK, where such rapid scale up is not occurring, provide comparison populations. In NHS Tayside, the following effective treatment services/pathways have been established: specialist nurse led hospital-based outreach services, embedded HCV treatment services in prisons, drug addiction centres and needle/syringe exchanges, and community pharmacist led treatment for those on OST.

The Tayside region of Scotland, with a population of 417,000 residing in an area of 7519 km^2, has approximately 2,800 PWID (either actively injecting or on OST) of whom 30% (800) are chronically infected with HCV. Accordingly, treating 570 will reduce the prevalence to below 10%; if the modelling results are borne out, HCV incidence will be reduced to below 1% from a current starting point of around 10%. Repeat HCV testing surveys of PWID in Tayside and elsewhere in Scotland/UK, conducted every one-two years, will monitor the impact of this "treatment as prevention" intervention in the context of harm reduction services—injection equipment and opiate substitution therapy provision—continuing to function optimally.

Prevention: Research

Action Plan generated research and evaluation findings of international significance include:

- Further evidence supports the hypothesis that only optimal "high coverage" harm reduction interventions (injection equipment and opiate substitution therapy) can appreciably reduce hepatitis C transmission among PWID (22, 23, 24).

- In the context of one of the largest prison studies ever conducted, findings indicated that opiate substitution therapy given to inmates had a profound beneficial impact on injecting behaviour and hepatitis C transmission (25); this was particularly important in view of prison officer resistance towards sanctioning the evaluation of a trial of injection equipment provision in a Scottish prison.

  Evidence indicates that the risk of hepatitis C transmission is elevated immediately following prison release. (26)

- Ground breaking modelling work proposed, and quantified the benefit of, the concept of antiviral therapy for infected active PWID to prevent onward HCV transmission (27, 34).

5.3 Diagnosis and Access to Specialist Care (21, 50, 51, 52)

Impact of the Action Plan on Diagnosis

The impact of the Action Plan on diagnosis of hepatitis C has been considerable. In 2006, 38% of Scotland's estimated 38,000 infected people had been diagnosed (53, 55); by 2018, the proportion was 50% of an estimated 21,000 (Figure 2). This increase appears modest but it does not take account of the thousands of people who have been diagnosed, successfully treated and thus are no longer living with hepatitis C. More striking and more relevant is the 55% reduction in the estimated number of infected people unaware of their infection (i.e: 23500 in 2006 compared to 10500 in 2018). Several factors account for these observations; these include i) the implementation of "user friendly" dried blood spot sampling of PWID in harm reduction/ drug treatment settings, ii) numerous local and national awareness raising events/campaigns involving third sector(Hepatitis Scotland and the UK Hepatitis C Trust) and statutory organisations and iii) the more general awareness spin-off of having several hundred people in a relatively small country working together on the common aim of addressing the country's hepatitis C problem. Nevertheless very considerable case finding challenges exist; those left undiagnosed, constitute the "higher hanging fruit" – especially large numbers of former PWID, not in regular contact with drug services, who often have multiple co-morbidities including those associated with excessive alcohol consumption.

Case Finding Strategy to Date

The hepatitis C case finding strategy in Scotland to date has been an opportunistic, targeted one-principally focused on people with traditional risk factors including i) injecting drug use (past or present), ii) a history of blood/blood factor transfusion pre October 1991, iii) originating from a high prevalence country (particularly Pakistan) and iv) an otherwise unexplained raised alanine aminotransferase liver enzyme level. The bulk of hepatitis C testing is undertaken in hospital and primary care settings but, in recent years, a policy of offering all prison inmates testing for blood borne viruses has increased the number of diagnoses and re-diagnoses made in that setting.

Birth Cohort Screening Consideration

Currently, modelling work is being undertaken to evaluate the potential cost effectiveness of the birth cohort screening approach --one that is recommended in the United States (56); such an approach, however, is more suited to a country with a risk factor profile which is mixed or weighted towards nosocomial origins because of the inability to narrow the risk down for targeting purposes. Nevertheless, it is very possible that, with continual reductions in drug treatment costs, coupled with the high effectiveness of such therapy and the low costs of its administration, a population based screening approach, perhaps restricted to

high hepatitis C prevalence geographical areas within Scotland, might be highly cost effective; however, that is not necessarily to say that such an approach will be affordable.

Access to Specialist Care

From an access to specialist care perspective, Scotland's Action Plan experience has demonstrated the enormous challenge of transporting highly vulnerable people along the patient highway of care; the proportion of the diagnosed population in specialist care year on year during the action plan period barely exceeds the 40% mark. Failure to i) get referred to, ii) comply with referral to, or iii) maintain a relationship with specialist care has severely hampered the country's hepatitis C efforts. One health board area (Tayside, incorporating the city of Dundee) in Scotland, serving 7**%** of the country's hepatitis C infected population, has developed a non-traditional diagnostic and care service; recognising the different needs of infected people, a bespoke approach, involving the tailoring of services to the individual, has been adopted (see case study above). Examples of such an approach are now evident in other parts of the country. Depending on the circumstances and the needs of the person, care from diagnosis through to treatment is provided in a single or a combination of secondary, primary or other community (including pharmacy, harm reduction, drug treatment and prison) setting(s). The team responsible for this "taking the service to the people" model are driven, collectively, by a vision of a hepatitis C free Tayside in the near future. Consequently, Tayside diagnosis and treatment uptake rates are the highest in the country and its paradigm is considered, nationally and internationally, to be outstanding.

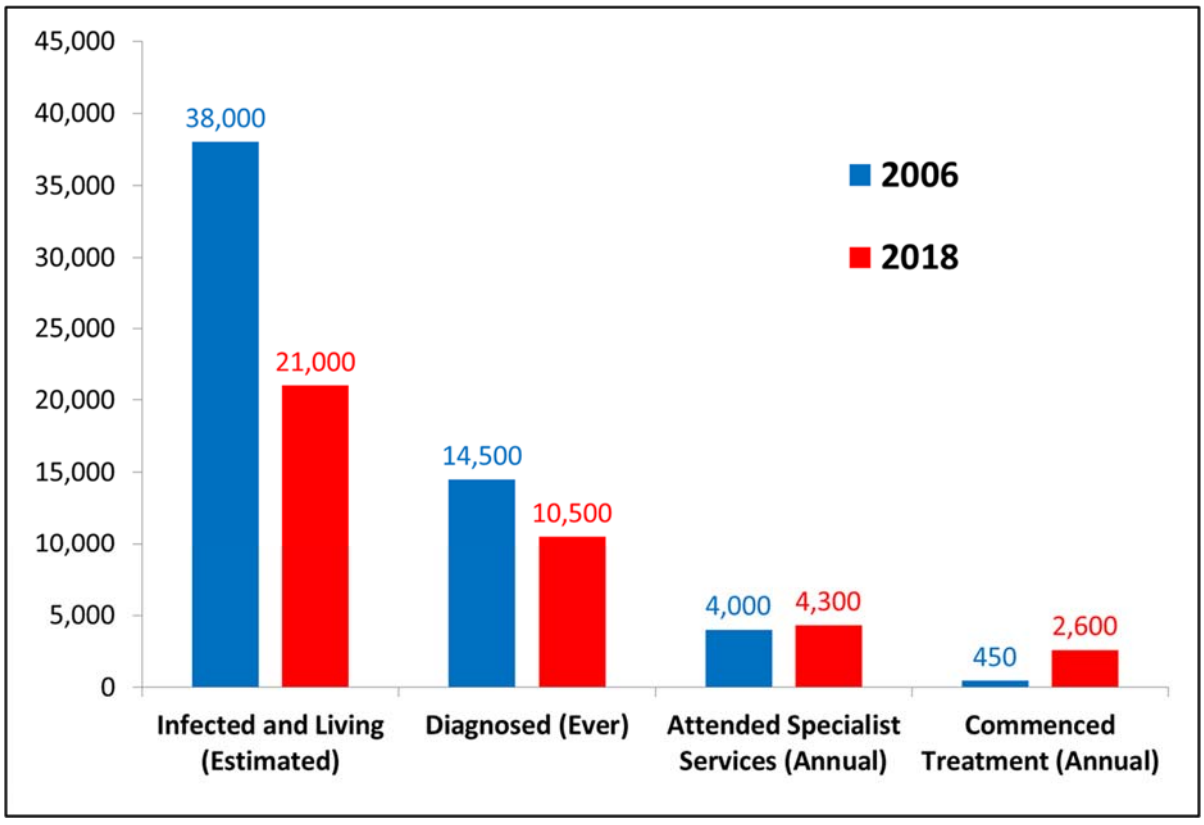

Figure 2: Change in the Chronic Hepatitis C Landscape between 2006 and 2018 (Source HPS/GCU)

Diagnosis and Access to Care: Research

Action Plan generated research and evaluation findings of international significance include

- Experience demonstrated the acceptability and utility of fingerprick blood sampling onto filter paper by non-clinical staff in non-clinical (e.g. harm reduction and mosque) settings in identifying infected PWID and migrants from high HCV prevalence countries (29, 31, 32).
- Evidence supports the hypothesis that knowledge of one's own HCV status, per se, leads to a reduction in quality of life additional to that stemming from any HCV-related disease (33).
- Observations show how difficult it is to encourage many primary care practitioners to test for, and diagnose, infection particularly among former PWID of whom many have advancing disease (9, 30).
- Rates of successful passage through the referral, assessment and treatment pathway by PWID and other vulnerable people can be improved if social and addiction work support is provided as part of an integrated, multi-disciplinary and multi-agency care approach (36, 37).
- Interferon-based regimens, coupled with the prospect of shorter, safer, easier to administer non-Interferon ones (now available), have been barriers to treatment uptake (43).
- A predominantly consultant co-ordinated, specialist nurse-managed clinical service can be both effective and efficient.
- Interferon-based regimens, can be administered successfully in community care settings (36, 61); these observations indicated that there would be little problem with Interferon-free ones.
- It is possible to provide equity of access to HCV treatment and care for hepatitis C-infected people with co-morbidities, particularly addiction problems, and those residing in rural areas or in prison (36, 47)

5.4 Treatment (21, 50, 51, 52)

Treatment Targets

The impact of the Action Plan on antiviral treatment uptake has been profound. To ensure that additional funding dedicated to treating people was spent on that purpose, annual treatment number targets were set. These have risen over time from 500 in 2008/9 to 2000 in 2018/19 (Figure 3). The targets, both national and health board area (calculated by factoring the sizes of the total and hepatitis C infected populations), have been taken seriously, generally being met and usually being exceeded.

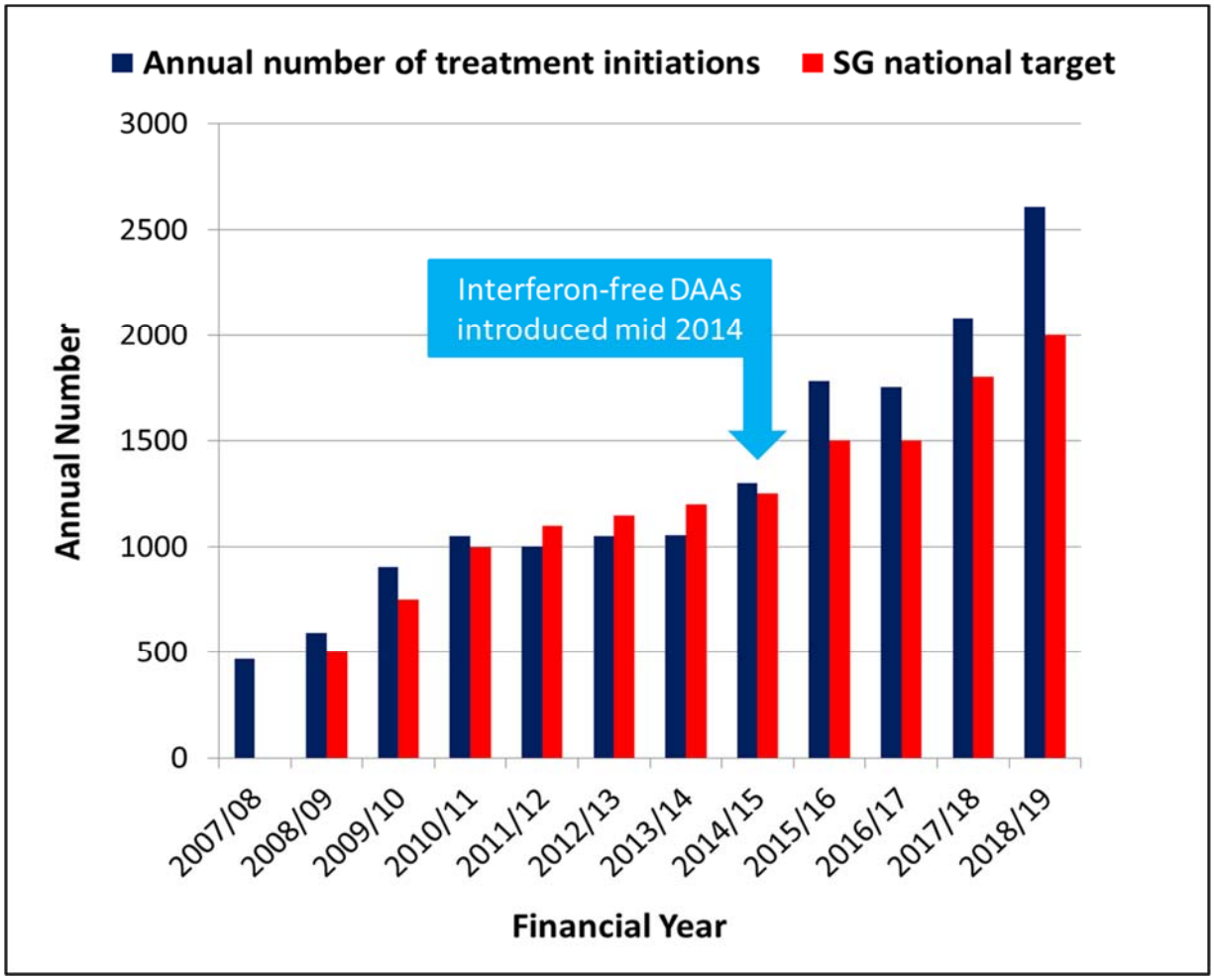

Figure 3: The annual number of patients initiated on HCV antiviral therapy in Scotland, and associated Scottish Government target, during financial years 2007/08 to 2018/19 (Source HPS/GCU).

Treatment-Induced Clearance of Infection

Not only have the numbers treated increased but the proportion of those treated having a successful outcome has also increased – from just over 70% in 2010/11 to in excess of 95% since 2015/16 – as a consequence of the movement away from injectable interferon-based regimens to all-oral, safe Direct Acting Antiviral(DAA) therapies in mid 2014 (57). Critically, these new agents are highly effective in people with cirrhosis (Figure 4).

This progress over the Action Plan lifespan (2006-2018) is best demonstrated by the estimated cumulative numbers of infected people treated and treated successfully – 16,000 and 12,800, respectively.

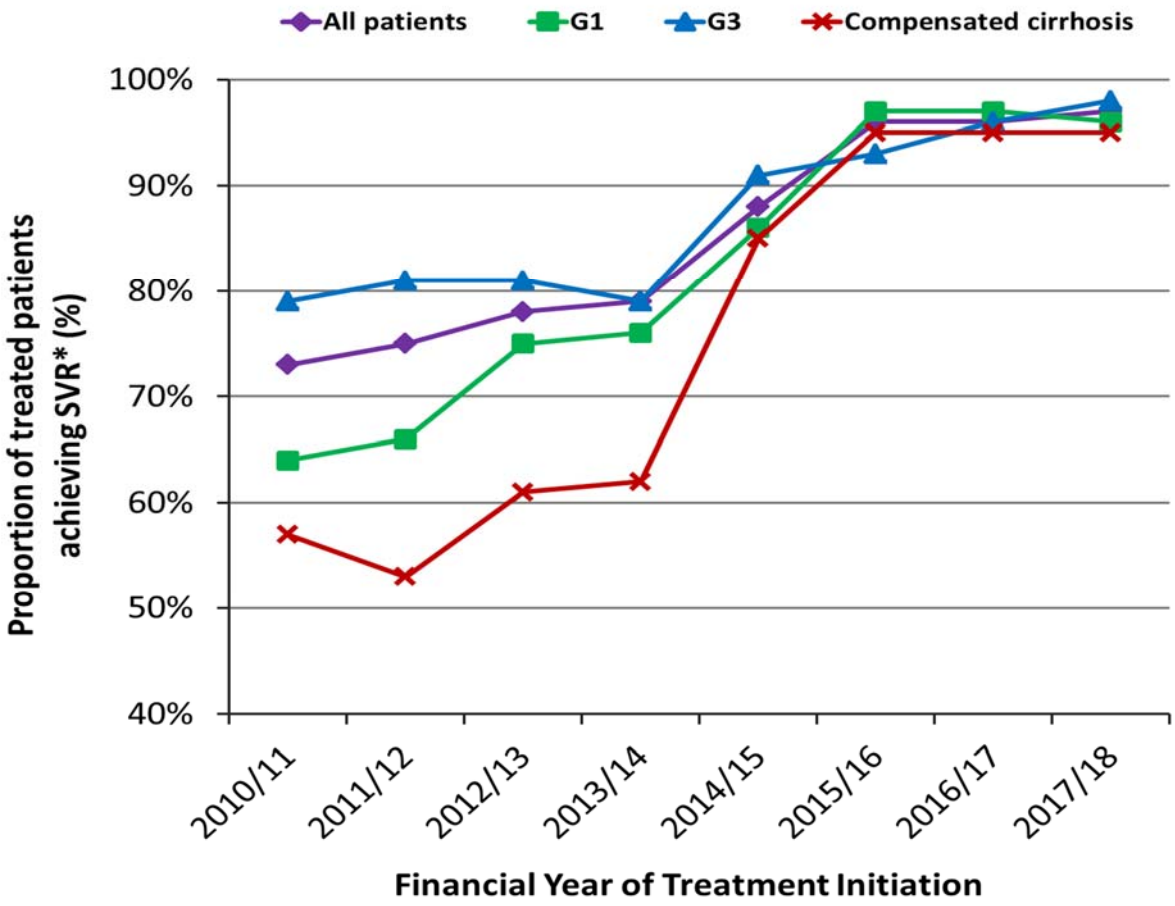

Figure 4: Impact of the Scottish Strategy on Response to HCV therapy (Source: HPS/GCU)

Prioritisation of Treatment

Another feature of recent hepatitis C government policy was its introduction of treatment prioritisation criteria. During the pre-DAA Action Plan era, 60% of treated people had no or mild liver disease – an understandable proportion in the context of interferon/ribavirin based treatment regimens which were more effective in those without cirrhosis or severe fibrosis of the liver. In 2015, the Scottish Government introduced the policy of prioritising therapy, in terms of timing only, for those with moderate to severe liver disease (58). This policy, did not exclude people with no, or mild, liver disease from being treated but it did change the distribution of the no/mild: moderate/severe liver disease ratio from approximately 60%:40% to 40%:60%, respectively. The policy of prioritization, since removed in April 2018, was introduced to ensure that, in the context of DAAs being very costly but highly effective in people with advanced liver disease, Scotland would realise optimal “bang for buck” and would have a real chance of reducing the incidence of hepatitis C-related liver failure by 75% by 2020; this new morbidity target was set by the Scottish Government in 2015 in response to the inaugural World Hepatitis Summit’s Glasgow Declaration (September 2015) to eliminate hepatitis C as a serious public health concern (3). Critically the policy was an evidenced–based one, underpinned by statistical modelling work indicating that 1500 people

with moderate to severe HCV - related liver disease would need to be treated annually during this period (46).

Treatment: Research

Action Plan generated research and evaluation findings of international significance include:

- In the context of rapid scale-up of therapy, former and active PWID, including prison inmates, can be treated without any SVR compromise (38, 47 63).
- No clinically significant impairment in SVR achievement in the “real world” clinical setting, relative to randomised clinical trials (35).

5.5 Burden of Infection and Disease

Infection

The impact of the Action Plan on the infection and disease burden has been considerable. Regarding the number of people infected with chronic hepatitis C, the provisional estimate for 2018 is 21,000 (range 16000-26000) - a 17,000 (45%) reduction on the 2006 one of 38,000. The rate of decline in prevalent infection has only recently started to accelerate due to the increasing Scottish Government treatment targets, the introduction of the DAAs and the possible decline in the size of the PWID population susceptible to infection.

Burden of Disease

Regarding the burden of disease, the principal outcome indicators are hepatitis C-related liver failure (Decompensated Cirrhosis (DC)), Hepatocellular Carcinoma (HCC) and death as a consequence of DC and/or HCC.

Decompensated Cirrhosis (DC) i.e: Liver Failure

Between 2006 and 2013, the number of individuals with chronic hepatitis C at the time of presentation with DC increased from 71 to 141 (Figure 5) (53); it was predicted that the annual number would have continued to rise to at least the year 2030 in the absence of the DAA therapies (17). With the introduction of such treatment in mid 2014, however, the number of DC presentations declined by 67% to 47 in 2018. This reduction is consistent with the number of people with compensated cirrhosis treated over this period and a compelling justification for Scottish Government policy which advocated the prioritisation of treatment for people with more severe liver disease. On a slight note of caution, an emerging upward trend in the number of people developing liver failure after hepatitis C virus clearance has been observed; the numbers, however, are relatively small.

The life time cost of managing a case of liver failure from the date of presentation is estimated at around £95,000. Related to the large number of people with HCV-related serious liver disease (i.e: people with cirrhosis but not liver failure) that have been treated and have achieved viral clearance (estimated 1,600) during the four years since the introduction of the new DAA therapies, it is estimated that approximately 330 cases of liver

failure could have been averted over this period (66). This translates to a potential avoidance of in excess of £30 million to the NHS in caring for patients with liver failure, over and above the obvious humanitarian gains (Source: HPS/GCU).

Hepatocellular Carcinoma (HCC)

(51) For people with severe fibrosis, compensated cirrhosis or decompensated cirrhosis, it is evident that an SVR may reduce but cannot completely eliminate the excess risk of HCC as irreversible damage has already been done. Further, an SVR, by increasing longevity among those with cirrhosis in particular, is increasing the pool of people susceptible to developing HCC. The number of people with chronic hepatitis C at the time of HCC presentation rose from 19 in 2006 to 58 in 2016; by 2018, however, the number of new presentations of HCV-related HCC fell dramatically by 69% to 18. This highly encouraging observation suggests that treatment is conveying a serious HCC preventative impact.

Death due to DC or HCC

The number of people with chronic hepatitis C at the time of death for which there was a mention of DC and /or HCC on the death certificate increased from 33 to 67 between 2006 and 2015; since then, a 49% decrease in the number to 34 has been observed.

These declines in hepatitis C-related DC, HCC and death, almost certainly, have arisen as a consequence of thousands of people with advancing liver disease having being treated with the new therapies over the last 5 years and auger well for a relatively near future where such serious outcomes are a rare event.

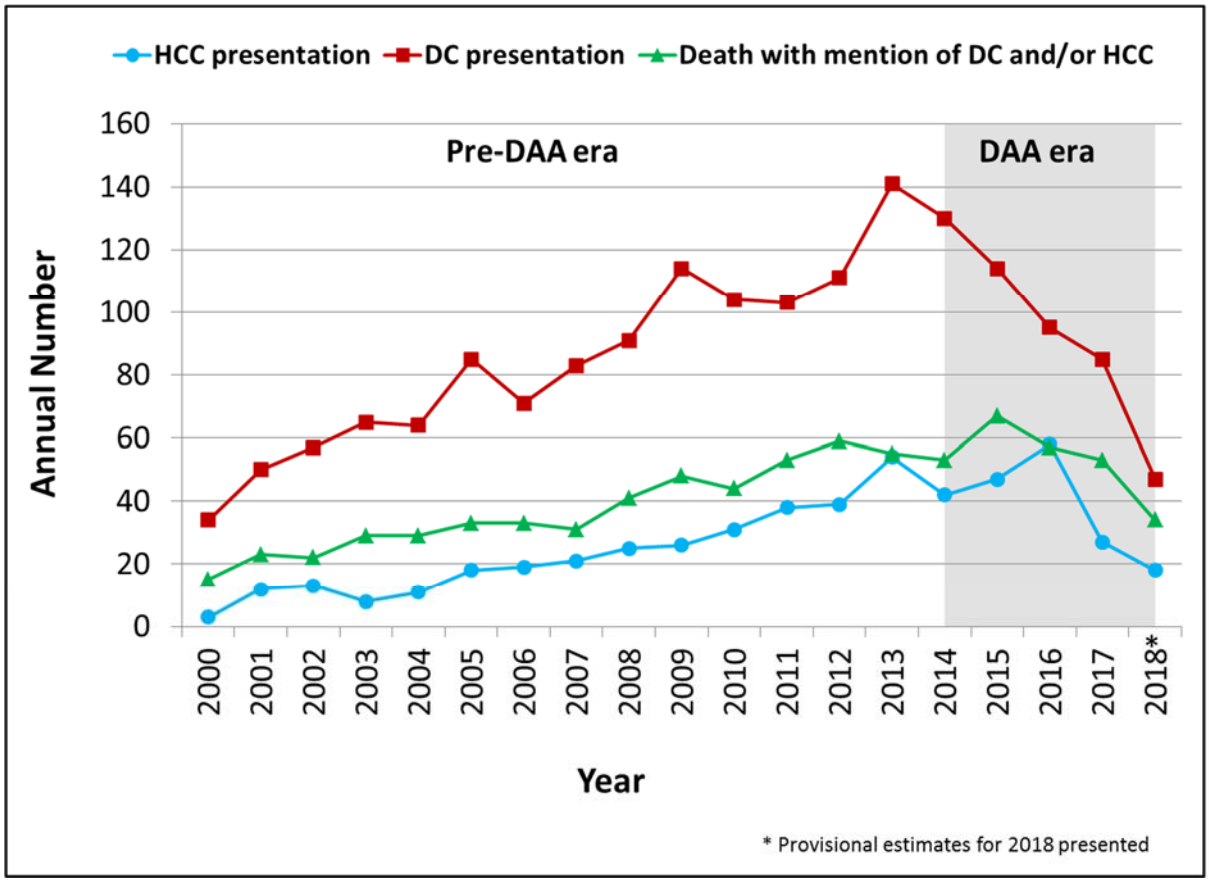

Figure 5: New Presentations of Decompensated Cirrhosis (DC) and Hepatocellular Carcinoma (HCC), and Deaths from DC and/or HCC among People with Chronic Hepatitis C Infection (at time of presentation) in Scotland: 2000-2018 (Source HPS/GCU)

Burden of Infection and Disease: Research

Action Plan generated research and evaluation findings of international significance include:

- SVR is strongly associated with a reduction in liver disease morbidity and mortality, and also mortality and morbidity due to extrahepatic conditions including circulatory diseases. (39, 40).
- Despite these favourable associations, patients with SVR still die at almost twice the rate of the general population. Behaviour factors – particularly drug use and alcohol use - are strong determinants of mortality risk in this population (40-43).
- In the context of the Interferon treatment era, re-infection among PWID following SVR does occur but probably at a lower rate that that observed among an untreated population (44, 45).
- Modelling work indicates that the potential benefits of an SVR are highly influenced by age and disease stage at time of therapy – findings which support the view that while everyone who wants therapy probably needs it, the urgency of need for some is critical (49).
- There is no evidence that DAA therapy, per se, increases the risk of developing hepatocellular carcinoma (HCC); increasing longevity in individuals who, otherwise, would have died from hepatitis C, increases HCC risk (48).
- Modelling work demonstrated the short and longer term impacts on infection and liver disease reduction from prioritising DAA therapy on the basis of disease stage (46, 49).

6 Proposed Scottish Government Strategy (2019) to Achieve Elimination of both Infection and Disease

6.1 The Strategy

Current Strategy

In the wake of the introduction of the new DAAs, the Scottish Government announced, in 2015, its intention to “eliminate hepatitis C as a serious public health concern”. Informed by modelling work (46), a burden of disease target, in addition to a treatment one, (see above) was introduced and treatment was prioritised for those with more advanced liver disease;

further, health boards were encouraged to i) adapt their models of hepatitis C management from a hospital based one to one more positioned in the community/ primary care setting, and ii) increase efforts to identify those undiagnosed and those previously diagnosed but now lost to or never in specialist follow-up - especially older individuals more likely to have advancing disease. Accordingly, the focus has been on reducing severe disease.

New Strategy: Lifting Prioritisation for Therapy and Improving Case Finding

The policy going forward will focus on not just the elimination of disease but also infection. To realise the vision of hepatitis C elimination, the government lifted, in April 2018, the 2015 recommendation on prioritising therapy for those infected people with moderate to severe liver disease and has reaffirmed its commitment to improving case finding and access to care; in 2017 it commissioned a Short Life Working Group to generate specific recommendations to intensify the effort to identify people who remain undiagnosed and ensure that people who are already diagnosed find it easy to access therapy, particularly in community settings; these were published in January 2019 (65)

New Strategy: Treatment Targets

It is proposed that the Government should set new long-term treatment number targets based on statistical modelling work generated by the HPS/GCU team(See Appendix1). Figure 6A shows the projected number of individuals living in Scotland with chronic hepatitis C infection according to the number treated during 2019-30. If, on average, approximately 3,000 people per year are treated from 2020, it is estimated that the threshold of 5,000 people chronically infected and living in Scotland would be reached in 2024.Scotland's Hepatitis C Treatment and Therapies Group of experts considered that having no greater than 5,000 people infected with hepatitis C would constitute the elimination of the infection as a serious public health concern.

For comparison, if 2000 or 4000 people were treated annually over the same period the Elimination date would be reached in 2027 or 2023, respectively

The Scottish Government has already approved the following minimum treatment target - 2500 in 2019/20- and it is proposed that it should set a minimum target of 3000 in 2020/21 and each year thereafter.

New Strategy: Serious Outcomes Targets

With respect to hepatitis C-related DC, HCC and death due to DC and/or HCC, the Government is committed to the elimination of such outcomes. As outlined above even if treatment targets are met or exceeded, some infected people who are successfully treated may still progress to such outcomes. Nevertheless, it is proposed that the government should set a target of less than 10 new presentations/deaths per year--among people with chronic hepatitis C at the time of presentation/death--for each of the three outcomes to be reached no later than 2024.

New Strategy: Prevention

The government is also committed to preventing people becoming infected in the first place. Such prevention, almost exclusively, applies to injecting drug use behaviours; accordingly, there should be no let up in the provision of optimal harm reduction measures – namely injection equipment provision and opiate substitution therapy. It is proposed that the Government should support the treatment of people who are actively injecting drugs and who are deemed, by clinicians, ready for antiviral therapy, and support the evaluation of such treatment as a means of preventing the onward transmission of infection.

6.2 Reasons Why the Strategy needs to be Ambitious

Scotland needs an ambitious hepatitis C elimination strategy for the following reasons:

- Since 2008 Scotland has been a world leader in responding to the challenge of hepatitis C, described in 2004 by Scotland's Minister of Health as "one of the country's greatest public health challenges". As a consequence Scotland, unlike most other countries, has the hepatitis C services and coordination infrastructure to take advantage of stunningly effective new therapies.
- The World Health Organization has called for the elimination of hepatitis C worldwide and uses the Scotland approach as a model for other countries to follow.
- The principal purpose of diagnosing and treating a hepatitis C infected person is to prevent them from progressing to life threatening diseases (liver failure and/or liver cancer). Because hepatitis C is an insidious infection with a long incubation period, people often present to hospital when it is too late. Accordingly, the best approach, by far, to managing hepatitis C--other than preventing people getting infected in the first place--is to diagnose and treat everyone as early as possible. This approach, undoubtedly, provides the best possible chance of avoiding serious hepatitis C-related liver disease.
- Compelling evidence indicates that hepatitis C, regardless of liver disease stage, is associated with mental health problems such as depression and anxiety; these problems improve following the clearance of virus.
- Thousands of people remain undiagnosed and thousands of diagnosed people have treatment. Most are vulnerable individuals with co-morbidities and sub-optimal living circumstances. To ensure that a highly effective, potentially life changing, intervention is made accessible ,services must reach out to these people in a highly proactive way; waiting for infected people to turn up at the specialist clinic door, often with end stage liver disease, is unacceptable.
- No other condition is more associated with deprivation than hepatitis C; accordingly, addressing hepatitis C intensively and urgently as proposed is an outstanding example of addressing inequality.
- If Scotland is to intensify its effort to identify people whose hepatitis C is undiagnosed and those diagnosed but lost to, or never in, clinical follow up, it is essential that an offer of treatment is made, regardless of liver disease status, and that there should be no undue delay in the administration of such therapy. Maximising the opportunity

of engagement must be taken; as evidenced by decades of experience, repeat engagement may only occur when it is too late to intervene effectively.

- It is likely that treating people who are continuing to inject drugs will convey not just an individual benefit but also a population one through the prevention of onward transmission of infection; the simultaneous evaluation of “hepatitis C treatment as prevention” is currently being undertaken in Tayside.
- Highly effective, safe and easy to administer therapies are approved by the Scottish Medicines Consortium and deemed highly cost effective at prices several-fold greater than current ones.
- The average cost of a course of therapy in 2018 lay within the £3000-9000 range – representing an approximate three to four-fold reduction since 2016; it is likely that the cost will decrease further in the years to come.
- By preventing the life-threatening consequences of hepatitis C – for example, an estimated 330 cases of liver failure have been averted during 2015-18 and thus over £30 million of expense avoided – more resources can be freed for other hepatitis C and non-hepatitis C related services.
- In addition to the humanitarian benefits of a more rapid approach to elimination, such an approach is likely to cost less, as indicated below.

6.3 Different Hepatitis C Treatment Strategies: Cost to the NHS

In the context of very appreciable reductions in the cost of direct acting antiviral therapies since their initial availability in 2014, it is reasonable to assume that the annual average cost of a course of therapy is unlikely to exceed £3000 for the period 2020-24; it is possible that the cost may be a bit more in the early years and a bit less in the later ones. This assumption, while not a guarantee, is supported by National Procurement Scotland.

One also has to account for the cost of clinically managing people infected with hepatitis C. As the prevalence of infection decreases each year, so does the annual cost of clinically managing people; this is because the numbers of people diagnosed with mild, moderate and severe disease who require hepatitis C care will be less. Accordingly, the general principle is that the faster the HCV elimination date is reached, the lower the clinical management cost incurred by the NHS.

Figure 6B and Table1 show the estimated overall costs of treating 2000,3000 or 4000 people per year from 2020, based on average annual cost for a course of therapy of £3000 (see Appendix 1 for details on statistical modelling). Costs include the NHS cost of treating and managing all diagnosed infected people at different stages of their disease process and the costs of the drugs; note that the overall cost excludes those associated with resources required to identify infected people either already known to be infected or not yet diagnosed.

The key message is that the overall cost to the NHS during 2020-23 varies little when comparing treatment scenarios; thereafter, a divergence in cost occurs.

During 2020-24, the average annual overall costs of treating 2000, 3000 or 4000 people are £18 million (92/5), £20 million (101/5) or £20 million (99/5), respectively. During 2025-30, the average annual overall costs of treating 2000, 3000 or 4000 people are £10 million (58/6), £6 million (36/6) or £5 million (31/6), respectively.

Accordingly, treating more individuals is more expensive in year one (2020) but the gap narrows year on year till 2023/24, due to less infected people needing clinical care, when there is a crossover with considerable cost avoidance thereafter.

The overall humanitarian and economic benefits of as rapid an approach to elimination as can be sustained are compelling; nevertheless, one must take into account the practicalities of identifying infected people and ensuring that they are ready for treatment. It is in this context that a 3000/ year minimum treatment target with an Elimination date of no later than 2024 is proposed.

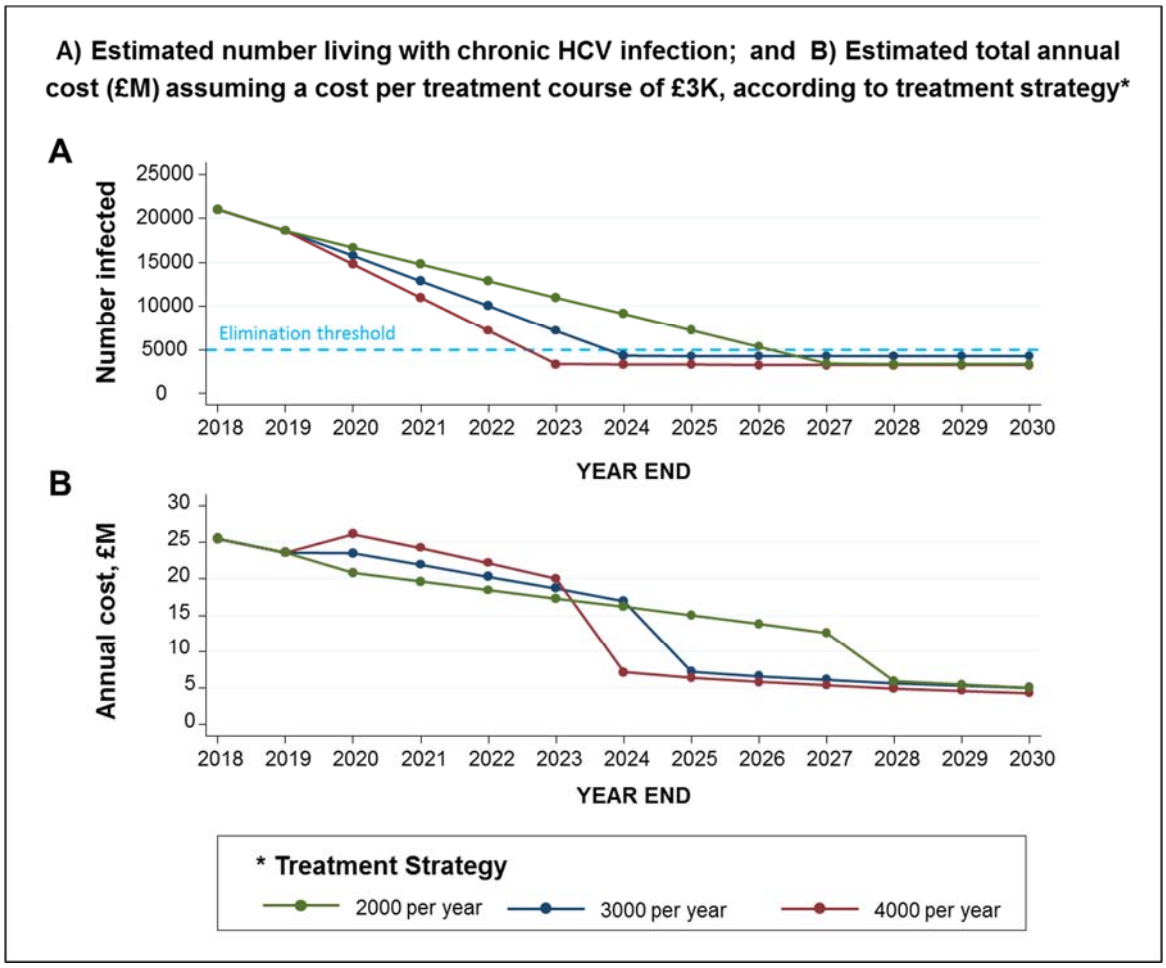

Figure 6: Predicted time when the elimination of infection date will be reached, and estimated overall annual cost to the NHS: depending on numbers treated/yr from 2020 (Source HPS/GCU--Based on models developed by Innes et al.Gut 2015 (Ref 46).

YEAR	2000/yr Treated Cost £million		3000/yr Treated Cost £million		4000/yr Treated Cost £million	
	Treatment	Overall	Treatment	Overall	Treatment	Overall
2020	6	21	9	23	12	26
2021	6	20	9	22	12	24
2022	6	18	9	20	12	22
2023	6	17	9	19	12	20
2024	6	16	9	17		7
2025	6	15		7		6
2026	6	14		7		6

Table 1: Estimated Annual Cost of Managing People with Chronic Hepatitis C Depending on Different Treatment Number Scenarios: 2,000, 3,000 and 4,000/yr at an Average Annual Drug Cost of £3,000 per Course of Treatment

6.4 Alignment with WHO strategy

Scotland is cognisant of the 2030 WHO targets for elimination - from 2015, 90% of infected people diagnosed, 80% of people eligible for therapy treated, an 80% reduction in new infections occurring and a 65% reduction in HCV-related deaths (60).

From a new infection perspective, it is anticipated that the annual number of incident infections among PWID will have declined considerably over the next five years due to the expected decline in hepatitis C prevalence among active PWID. Also, it is hoped that the declining trend in the incidence and prevalence of injecting drug use will continue.

From a mortality perspective, the observed reductions in HCV-related liver failure, hepatocellular cancer and death since the introduction of interferon-free DAAs is hugely encouraging, providing realistic optimism that the WHO targets will not only be met but reached several years before 2030.

6.5 Proposal for the Scottish Government's (2019) Hepatitis C Elimination Strategy: Summary

Context

Scotland's Hepatitis C Action Plan, initiated during 2006-8, has had an enormous impact on tackling one of Scotland's major public health problems and has laid the foundations for the next equally ambitious phase of the Plan:

Achievements include:

Between 2006 and 2018:

- A 45% reduction in the number of people living with chronic hepatitis C from an estimated 38,000 to 21,000.
- A 55% reduction in the number of people unaware of their infection from 23500 to 10500.
- Approximately 16,000 treated of whom an estimated 12,800 (80%) have cleared their virus.

In the Context of the Era of the Direct Acting Antiviral Therapies, available since 2014:

- New presentations of hepatitis C related decompensated cirrhosis (liver failure) declining 67% from a peak of 141 in 2013 to 47 in 2018.
- New presentations of hepatitis C related hepatocellular carcinoma declining 69% from a peak of 58 in 2016 to 18 in 2018.
- Hepatitis C related deaths declining 49% from a peak of 67 in 2015 to 34 in 2018.

Vision

The elimination of hepatitis C infection and hepatitis C related severe disease and death as a major public health concern by 2024 at the latest.

Definition of Elimination

Infection

5,000 or less chronically infected people - i.e.: 1 in 1000 people or less.

Liver Failure/Liver Cancer/Death

For each outcome, less than 10 people with chronic HCV presenting per year.

Compliance with WHO Elimination Targets

Targets, set by WHO in 2016, for the elimination of Hepatitis C to be achieved by 2030, will be met by the dates as above.

Why

A more rapid approach to elimination will secure undoubted humanitarian benefits with less people experiencing mild, moderate and severe morbidity associated with, and less people dying from, hepatitis C related disease

Additionally, it is estimated that the overall costs associated with hepatitis C to the NHS are less if the time when elimination is reached is earlier rather than later.

How

NHS Boards, together with local authorities and third sector organisations, and supported by Health Protection Scotland should:

- Treat a minimum of 2,500 during 2019-20 and 3,000 people each year thereafter; it is predicted that this strategy will achieve elimination by 2024.
- Guided by the recommendations made by the SLWG on Hepatitis C Case Finding and Access to Care,intensify efforts to identify those people undiagnosed and to re-engage diagnosed people not in contact with hepatitis C services. An eclectic model of hepatitis C care – i.e. the provision of services in both hospital and community settings, tailored to the needs of the patient-should be adopted.
- Ensure that people who inject drugs have access to and take up i) optimal harm reduction services and ii) if deemed clinically ready, antiviral therapy to prevent the onward transmission of infection.

Facilitated by

- A mature web of national and local multi-disciplinary and uni-disciplinary networks established during the early years of the Action Plan.
- Government, public health, clinical and third sector leaders who have achieved outstanding outcomes to date
- A world renowned service infrastructure ideally placed to take advantage of highly effective, safe, easy to administer and increasingly less expensive therapies.
- Highly sophisticated information generating initiatives to monitor key outcome; this programme will need to be enhanced, incorporating general population prevalence studies, to ascertain with reasonable precision the performance of the strategy.
- A programme of research to evaluate the effectiveness of interventions designed to prevent both infection and HCV related disease.
- An Elimination Strategy Implementation Group comprised of experts from a wide range of disciplines
- An Elimination Strategy project management team

7 Conclusion

The Action Plan has demonstrated that a Government-backed well co-ordinated approach, clinically led, with appropriate investment can transform services and rapidly improve the lives of thousands. But while Scotland, relative to other countries, is now doing well on many performance indicators, serious challenges remain; with tens of thousands of people – a large proportion with moderate to severe disease – still eligible for therapy, and over a third remaining undiagnosed, this moment, a decade post Action Plan launch, is merely the end of the beginning. Scotland, however, unlike many other countries, is in a great position to take advantage of the hepatitis C therapeutic revolution which has delivered outstanding therapies that prevent serious hepatitis C-related disease (57).

Perhaps the greatest achievement of the Action Plan to date has been the creation of a highly developed HCV service infrastructure. A workforce of hundreds has been trained, is experienced and – guided by nationally agreed guidelines, standards and targets – functions in a coordinated and integrated, multi-disciplinary and multi-agency way. Accordingly, awareness levels among both general and at-risk populations are much improved.

Government commitment towards the elimination of hepatitis C-related severe disease is unstinting and the Plan is now embedded within Scotland's Sexual Health and Bloodborne Virus (BBV) Framework – a policy arrangement which recognised, and has realised, the potential synergies of strengthening the interface between BBV (particularly hepatitis C) and Sexually Transmitted Infection services.

Supported by research expertise, monitoring systems – including ones which can rapidly evaluate the immediate and longer term impact of different therapies administered in different settings to different populations – are tried, tested and robust.

The next phase will be challenging not least because of the size of the undiagnosed and diagnosed untreated populations. But thanks to strong leadership and dedication from people of all positions – political**,** professional and patient – Scotland is ready to take the next step in combating hepatitis C. The Odyssey continues towards elimination.

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Appendix 1

Estimating Numbers Infected and Costs of Clinical Care on the Basis of Different Treatment Number Scenarios

Estimates of the annual/cumulative cost for each strategy have been generated from the Scottish hepatitis C forward projection model (Innes et al. Gut 2015;64:1800-1809). This model reduces the natural history of HCV infection into multiple "health states" - e.g. chronic HCV infection according to liver disease severity, current intravenous drug use, HCV genotype, etc. Drawing on the robust epidemiological data available from Scotland, we were able to determine the number of people living in each "health state" in the year 2009. Then, through defining the annual rate at which people transition from one health state to another (data which is available from international research), the model is thus able to estimate the number of people in Scotland that will be living in each health state in *future* years. A key strength of this model is that it incorporates a dynamic transmission function; new "individuals" with recently acquired chronic HCV infection enter the model every year. In any given year, the number of individuals entering the model in this way varies, primarily, according to the number of PWID living with chronic HCV infection. As a result, all costing and prevalence estimates generated from this model take into account the benefits of antiviral treatment vis-à-vis reducing transmission of HCV infection. Another crucial strength, is that the parameters of this model can be readily changed and interrogated, allowing one to directly infer, for instance, how the number of infected individuals in future years varies according to treatment uptake and the case mix of the treated population.

To generate the above costings estimates for each strategy, we assigned a monetary cost to each health state in the model, in line with recent economic evaluations (Martin, et al. J Hepatol 2016). The set of clinical management costs used were £205 for no/mild liver disease, £1065 for moderate disease, £1691 for compensated cirrhosis, £13559 for decompensated cirrhosis and £40,633 in the first year following a liver transplantation (Wright, et al. Health Technol Assess. 2006 & Shepherd et al. Health Technol Assess 2007). The total annual cost is calculated as the cost spent on antiviral treatment in a given year + the cost of each health state. It should be acknowledged that the health state costs, as above, have not been further adjusted for inflation or discounting and that the model only applies to people diagnosed with hepatitis C; it is likely that people undiagnosed are incurring costs too. On the other hand the health state costs assume that people always attend outpatient appointments but we know that a proportion of people default from these.