Hepatitis C – From Discovery to Elimination in 40 years

Dr Daniel Forton PhD FRCP

Consultant Hepatologist and Reader in Hepatology
St George's Hospital, London

St George's
University of London

27 year old woman

1 week history of:

Anorexia, nausea, diarrhoea, fever, abdominal pain

PMH:

CKD and dialysis x 2 week

20u blood transfusions over preceding 6 months

SGOT (serum glutamic-oxaloacetic transaminase)	250
SGPT (serum glutamic-pyruvic transaminase)	440

Three further cases on dialysis unit (52, 55, 57 days later)

Sex	Age	SGOT	SGPT	Units blood
F	25	1600	1700	14
M	33	1600	>2000	11
F	23	14	148	15

- Case 1 was ill for 1 week before a diagnosis was made. During this time she and the patients in cases 2,3,4 had been in the habit, while being dialysed, of playing Scrabble, a game that involves the passing of a board and counters among the patients.
- The remaining patient who dialysed on the same nights did not join in the game and did not develop hepatitis.

Reprinted from ANNALS OF INTERNAL MEDICINE, Vol. 69, No. 1, July 1968
Printed in U. S. A.

Hepatitis in a Maintenance Hemodialysis Unit

JOHN B. EASTWOOD, M.B., JOHN R. CURTIS, M.B., ANTHONY J. WING, B.M.,
and HUGH E. DE WARDENER, M.D., F.R.C.P.

London, England

SUMMARY **Fourteen of 27 patients being treated with maintenance hemodialysis and 1 staff nurse from the general wards developed hepatitis between August 1966 and April 1967; 1 patient died. Eight of the attacks were anicteric and three of these, asymptomatic. No cases occurred among the nurses, technicians, and doctors of the Maintenance Haemodialysis Unit.**

Gamma globulin modified the disease in the patients and may have prevented it altogether in the staff. The epidemiology of the outbreak and the apparent efficacy of gamma globulin suggest that the epidemic may have been due to infectious hepatitis.

HEPATITIS may develop in both patients and staff of centers in which maintenance hemodialysis is performed. Up to 1966, there had been reported to the European Dialysis and Transplant Association 40 cases in about 480 patients undergoing hemodialysis in 65 units; there were 9 deaths (1). Among the staff of these units there were 64 cases of hepatitis with 3 deaths. In his report, Kerr (1) points out that the incidence of hepatitis in these groups is higher than would be expected in an unselected hospital population of the same size.

Particularly severe outbreaks have occurred in Manchester (2), Liverpool (3), and Brooklyn (4). Some dialysis units have been unable to expand as a result of hepatitis (1). It would seem important, therefore, that the details of each epidemic be made known. We report here an outbreak of hepatitis in the Maintenance Haemodialysis Unit, Fulham Hospital, London.

DIALYSIS TECHNIQUES

Dialysis is carried out on 6 nights a week, and each patient is dialyzed twice weekly on the same nights for a total of 28 to 32 hr weekly. The patients are therefore dialyzed in three groups with little contact between each group. A single-pass warm dialysis system using modified two-layer Kiil dialyzers is used (5). After each dialysis the polypropylene boards of the dialyzers are washed in Haemosol® (Meinecke & Co., Inc.), rinsed in tap water, and then reassembled with new cuprophane (PT 150) membranes. The membranes are prepared by soaking in a pan containing 3% acetic acid in pyrogen-free water. Both the blood and dialysate compartments of the dialyzers are filled with 2% formalin (0.8% formaldehyde) in pyrogen-free water and left for at least 2 hr. Immediately before the next dialysis the formalin is drained off, and the dialysate compartment is washed through with tap water. The blood compartment is washed through with normal saline and then primed with heparinized normal saline. Dialysis fluid is distributed to each bed station from a centralized supply system. In February 1967, batch tank preparation was superseded by a central proportioning system. The supply system and circuit are rinsed with water after each dialysis and then sterilized with 6% formalin (2.4% formaldehyde) for 1 hr. At weekends the formalin remains in the system for 24 hr.

Nurses and technicians wear gloves when dismantling, sterilizing, and reassembling dialyzers and when handling equipment that has been in contact with patient's blood.

TRANSFUSIONS

Up to October 1966, blood transfusions amounted to 2.6 units per patient month.

Received January 2, 1968; revision accepted March 20, 1968.

From the Department of Medicine, Charing Cross Hospital Medical School, Fulham Hospital, London, Eng.

Requests for reprints should be addressed to John B. Eastwood, M.B., Department of Medicine, Charing Cross Hospital Medical School, Fulham Hospital, London W. 6., Eng.

N.B. Paper written when hepatitis was sub-divided into 'Infections' and 'Serum' Hepatitis

This paper pre-dated 'Australia' antigen, Hepatitis A and B nomenclature, and C D etc.

IBE 16.9.15 In retrospect the disease described here was probably Hepatitis C.

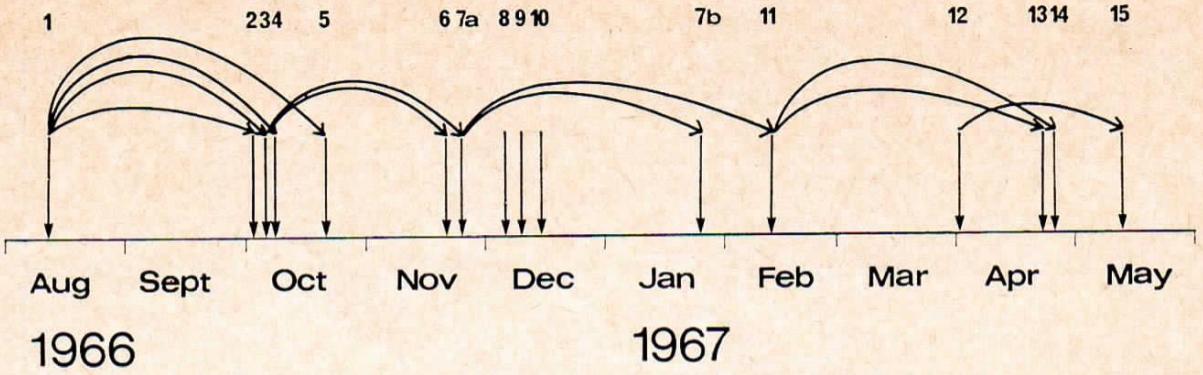


FIGURE 1. Diagram to illustrate the time relationships of the cases. Probable contacts responsible for the transmission of infection are shown by the curved arrows. Where there are no arrows, the contact is not known.

16 cases in total, 8 icteric, 8 anicteric

1 death – bronchial wall bleeding, liver was small, yellow and haemorrhagic with massive necrosis and heavy round cell infiltration of the portal tracts

Average incubation period was 55 days (range 42-71)

After case 1:

1. Certain modifications on nursing technique were made.
2. Gloves were worn by nurses during putting-on and taking-off procedures
3. Diposable cups, plates and cutlery were introduced
4. There was segregation of patients and staff for toilet arrangements
5. However meals continued to be taken in the unit by both patients and staff alike as there was no practicable alternative

same size.

Particularly severe outbreaks have occurred in Manchester (2), Liverpool (3), and Brooklyn (4). Some dialysis units have been unable to expand as a result of hepatitis (1). It would seem important, therefore, that the details of each epidemic be made known. We report here an outbreak of hepatitis in the Maintenance Haemodialysis Unit, Fulham Hospital, London.

Dialysis Techniques

Dialysis is carried out on 6 nights a week, and each patient is dialyzed twice weekly on the mantling, sterilizing, and reassembling dialyzers and when handling equipment that has been in contact with patient's blood.

Transfusions

Up to October 1966, blood transfusions amounted to 2.6 units per patient month.

Received January 2, 1968; revision accepted March 20, 1968.

From the Department of Medicine, Charing Cross Hospital Medical School, Fulham Hospital, London, Eng.

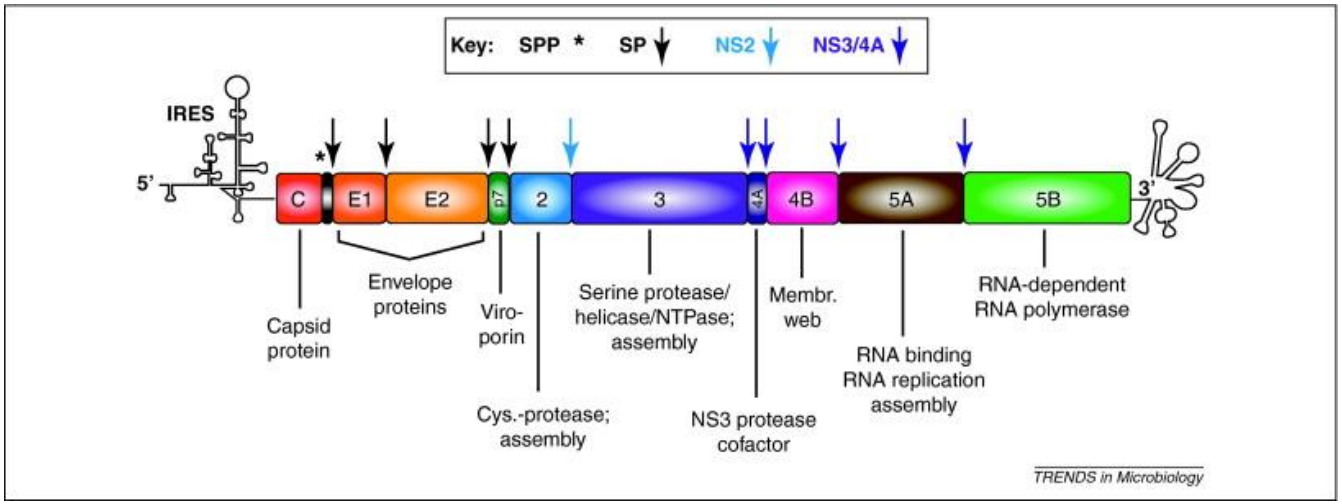
Requests for reprints should be addressed to John B. Eastwood, M.B., Department of Medicine, Charing Cross Hospital Medical School, Fulham Hospital, London W. 6., Eng.

N.B. Paper written when hepatitis was sub-divided into Infections and Serum Hepatitis

This paper pre-dated 'Australia' antigen, Hepatitis A and B nomenclature, and CD etc.

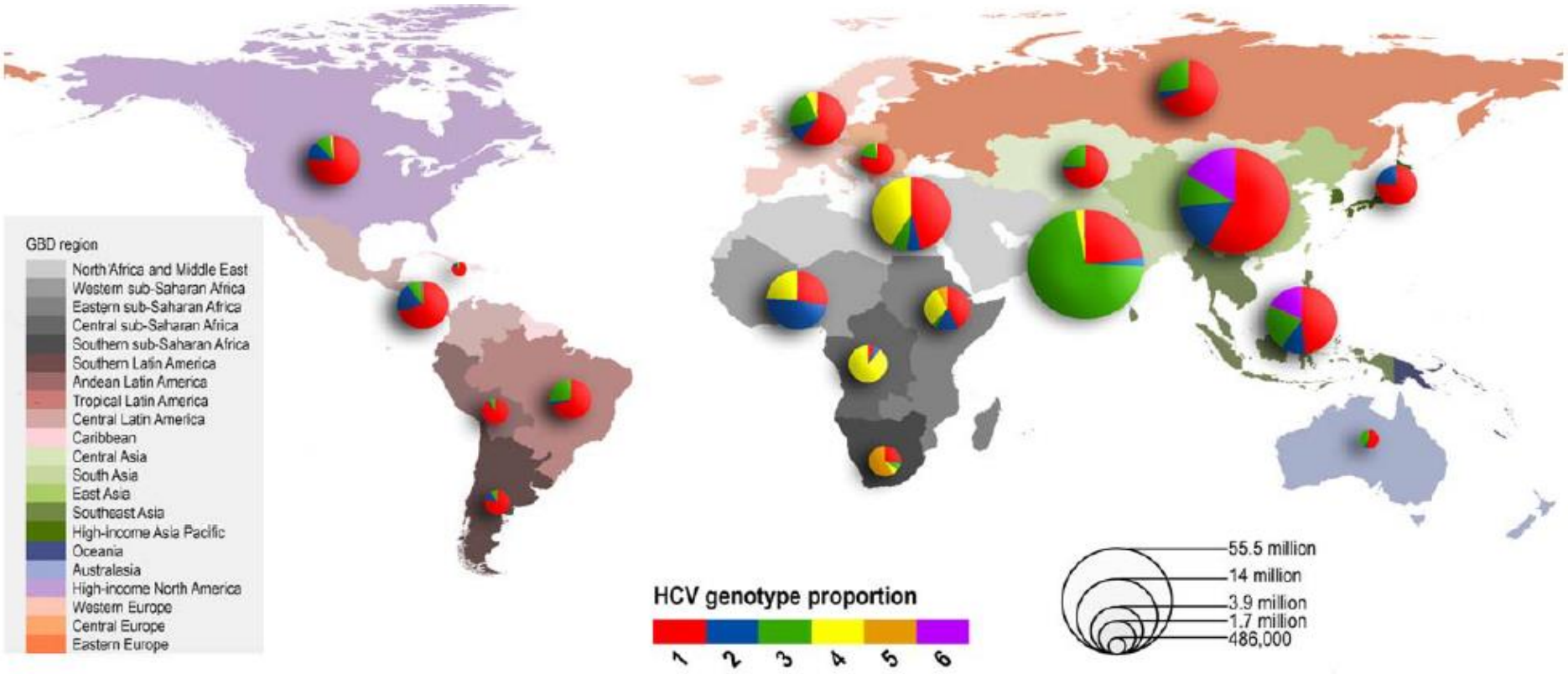
IDE 16.9.15 In retrospect the disease described here was probably Hepatitis C.

1989 HCV identified by isolation of a cDNA clone from NANB serum



HCV Burden and Global GT Distribution

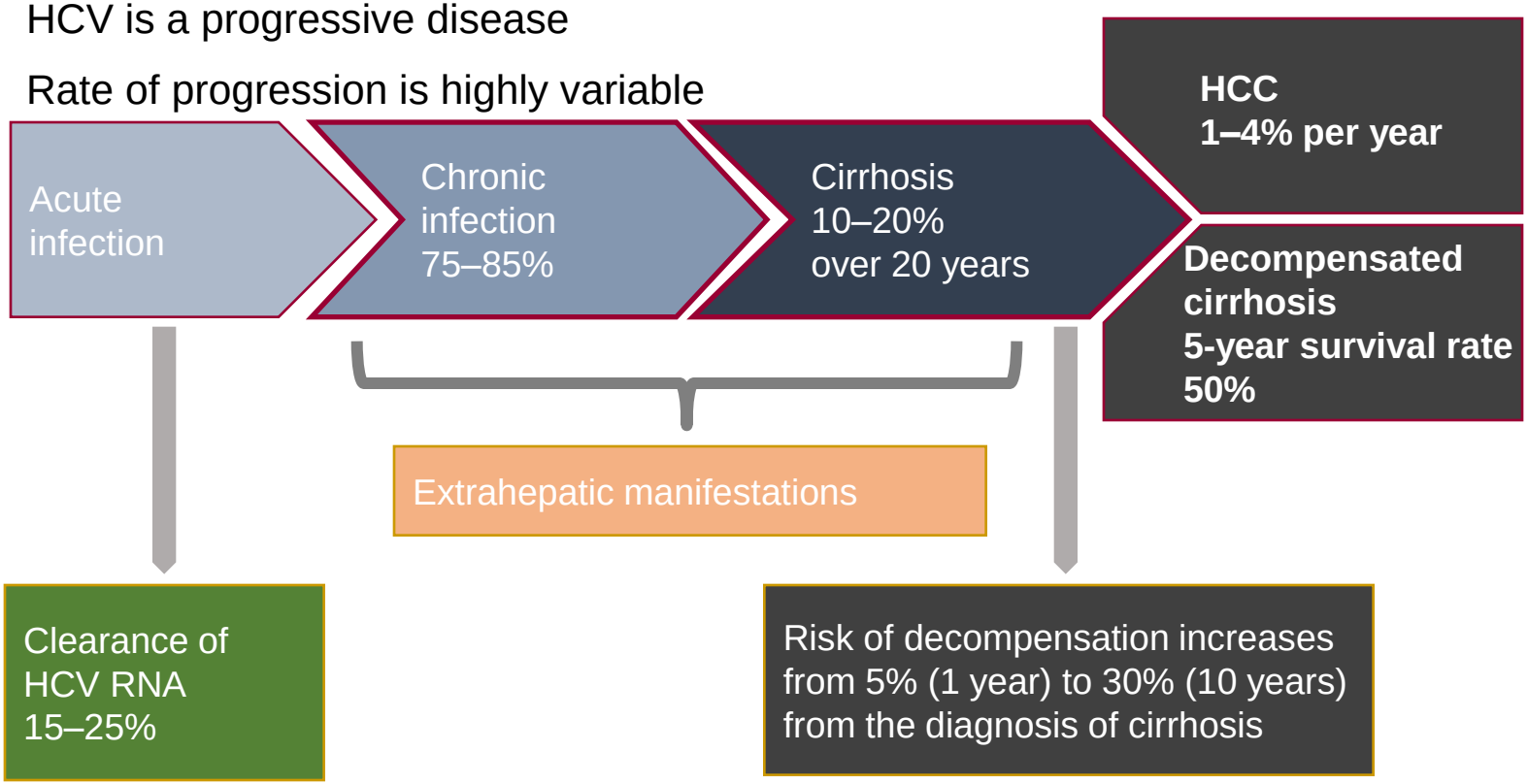
Around 9 million people in Europe are chronically infected with HCV



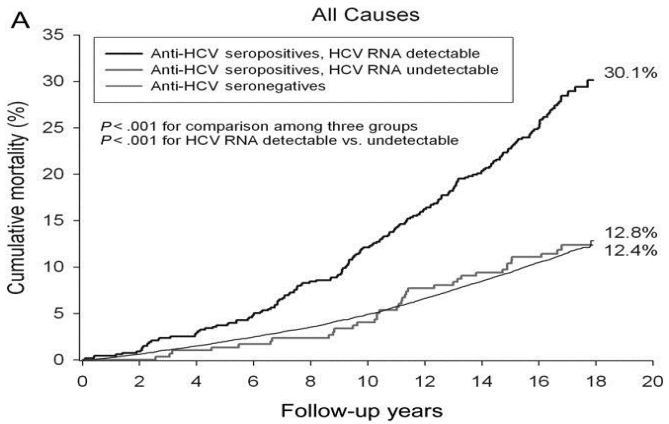
Messina JP, et al. Hepatology 2014; doi: 10.1002/hep.27259

HCV is a Progressive Disease with Serious Sequelae

- HCV is a progressive disease
- Rate of progression is highly variable

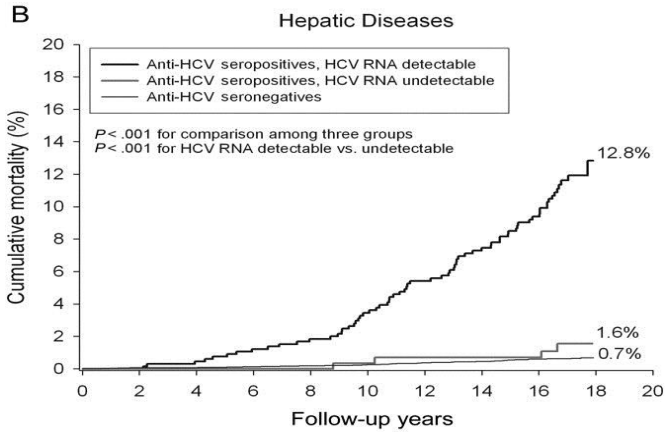


Adapted from Chen SL, Morgan TR. Int J Med Sci 2006;3:47–52



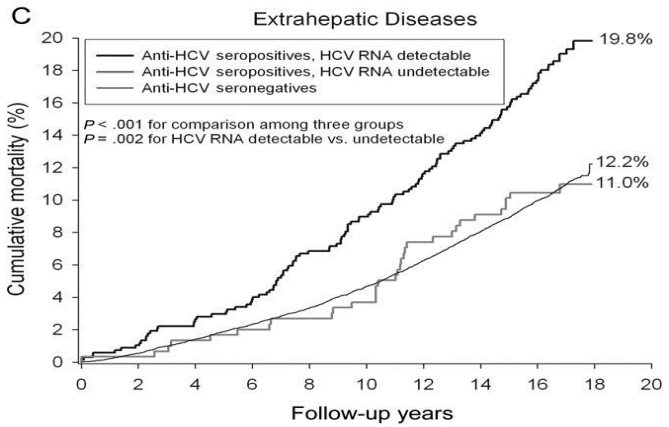
A. Cumulative mortality from all causes of death

Hazard ratio (HR) for mortality after 16.2 years of follow-up was 1.89 (1.66–2.15) for all causes.



B. Cumulative mortality from liver disease

HR for hepatic death was 12.48 (9.34–16.66), and



C. Cumulative mortality from extrahepatic causes

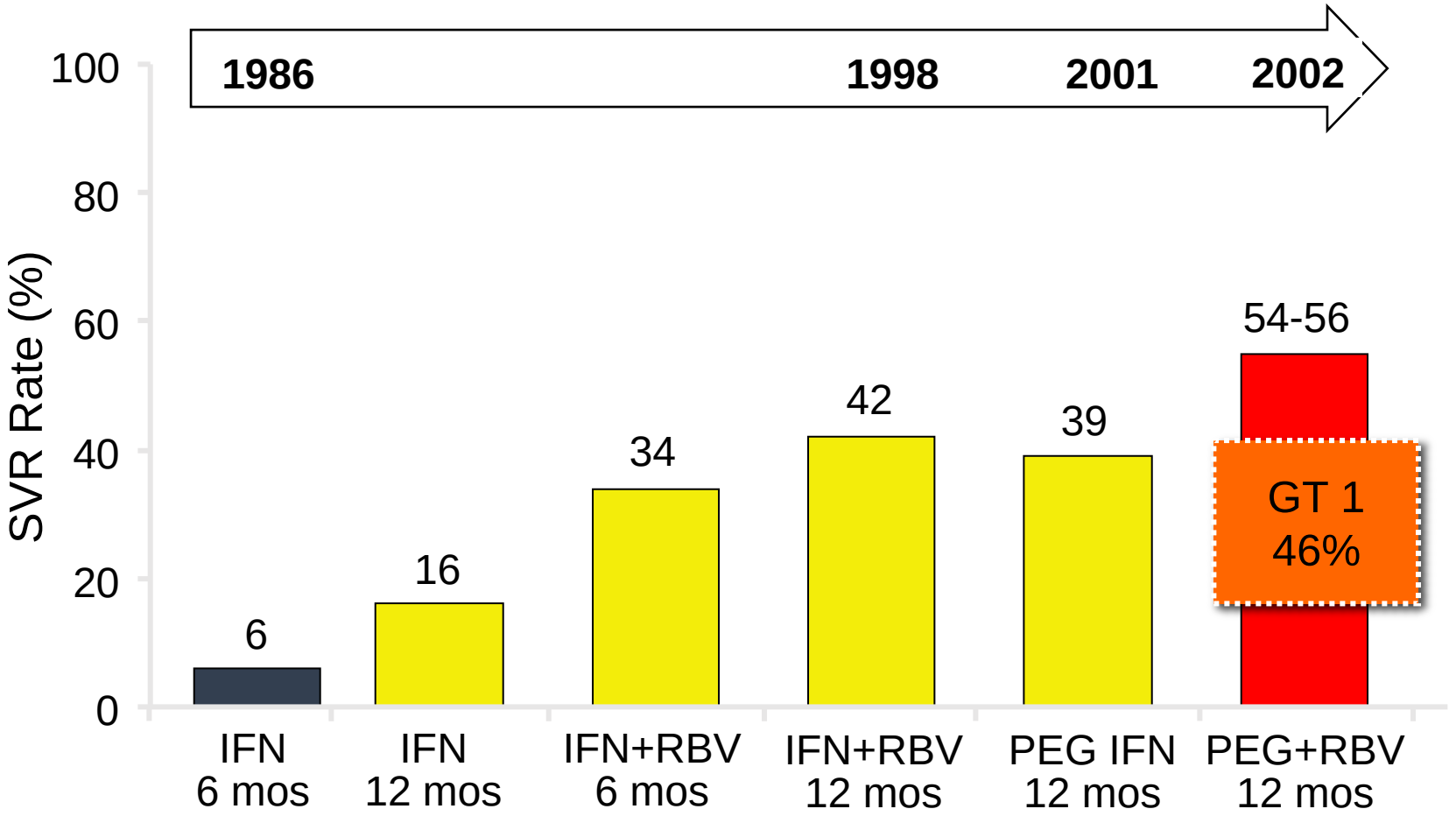
HR for extrahepatic deaths was 1.35 (1.15–1.59).

Lee M et al. J Infect Dis. 2012;206:469-477

1992 IFN-α licensed for treatment of HCV

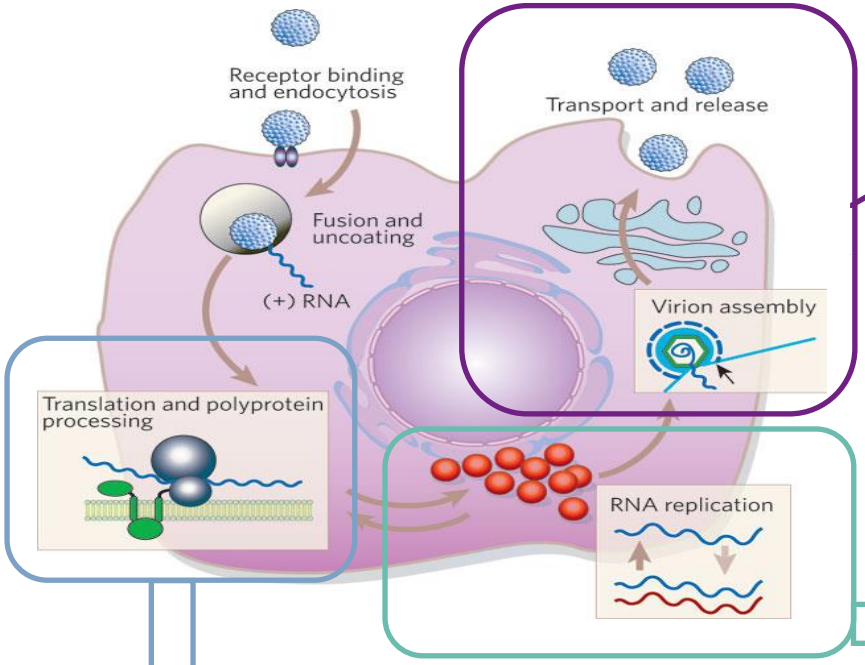
Outcomes were poor – 6% (24 weeks), 13-19% (48 weeks)

Progress was made by adding Ribavirin, and pegylation of interferon:



1. Strader et al. Diagnosis, management and treatment of hepatitis C. *Hepatology.* 2004;39(4):1147-1171.

Direct-Acting Antivirals for the Treatment of Hepatitis C Infection



NS5A inhibitor

- Ombitasvir (OBV)*
- Ledipasvir (LDV)†
- Daclatasvir (DCV)
- Elbasvir (EBR)‡
- Pibrentasir (PIB) §
- Velpatasvir (VEL)‖

NS5B polymerase inhibitor

- Sofosbuvir (SOF)† ‖
- Dasabuvir (DSV)*

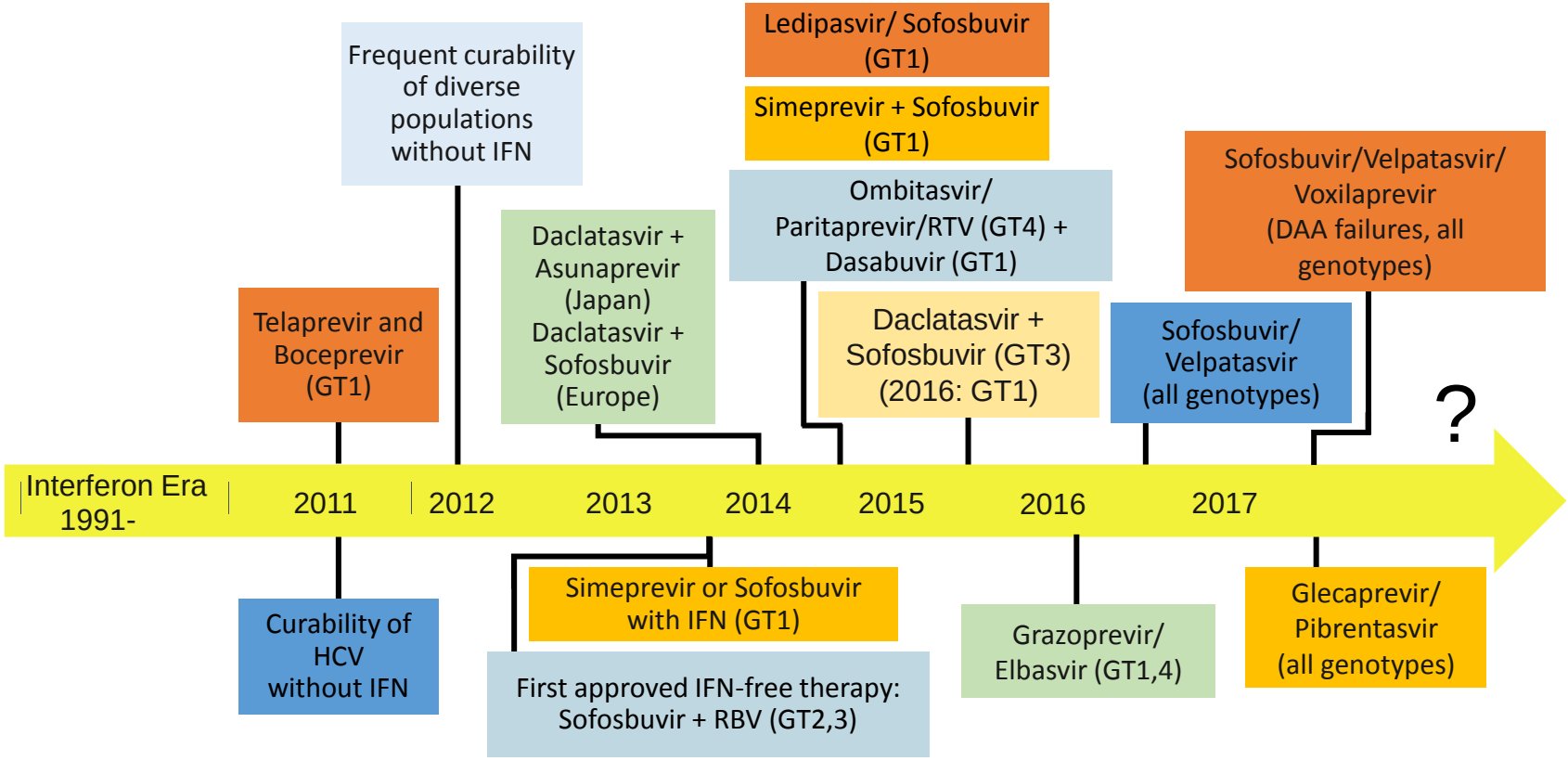
NS3/4A protease inhibitors

- Paritaprevir (PTV)*
- Simeprevir (SMV)
- Grazoprevir (GZR)‡
- Glecaprevir (GLE) §
- Voxilaprevir (VOX) §

* OBV/PTV/r co-formulated (Viekirax), DSV (Exviera); † LDV/SOF co-formulated (Harvoni);
‡ EBR/GZR co-formulated; ‖ SOF/VEL co-formulated; § Investigational treatments

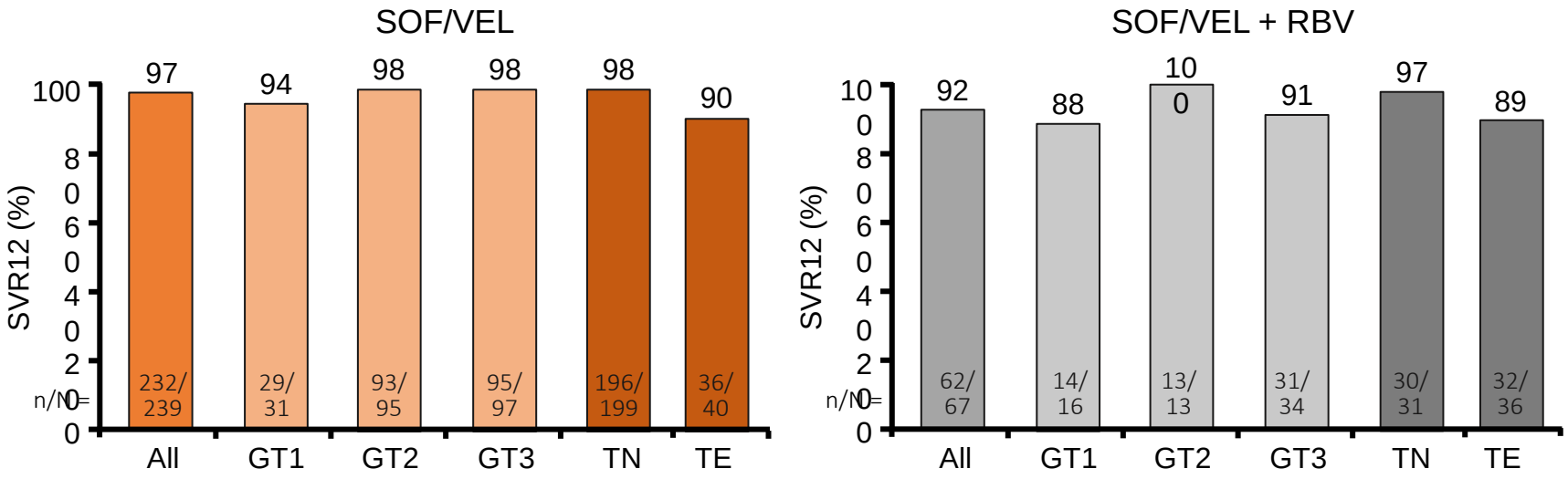

GILEAD
$1,000
PER PILL
SHAME!

The Evolution of HCV Therapy



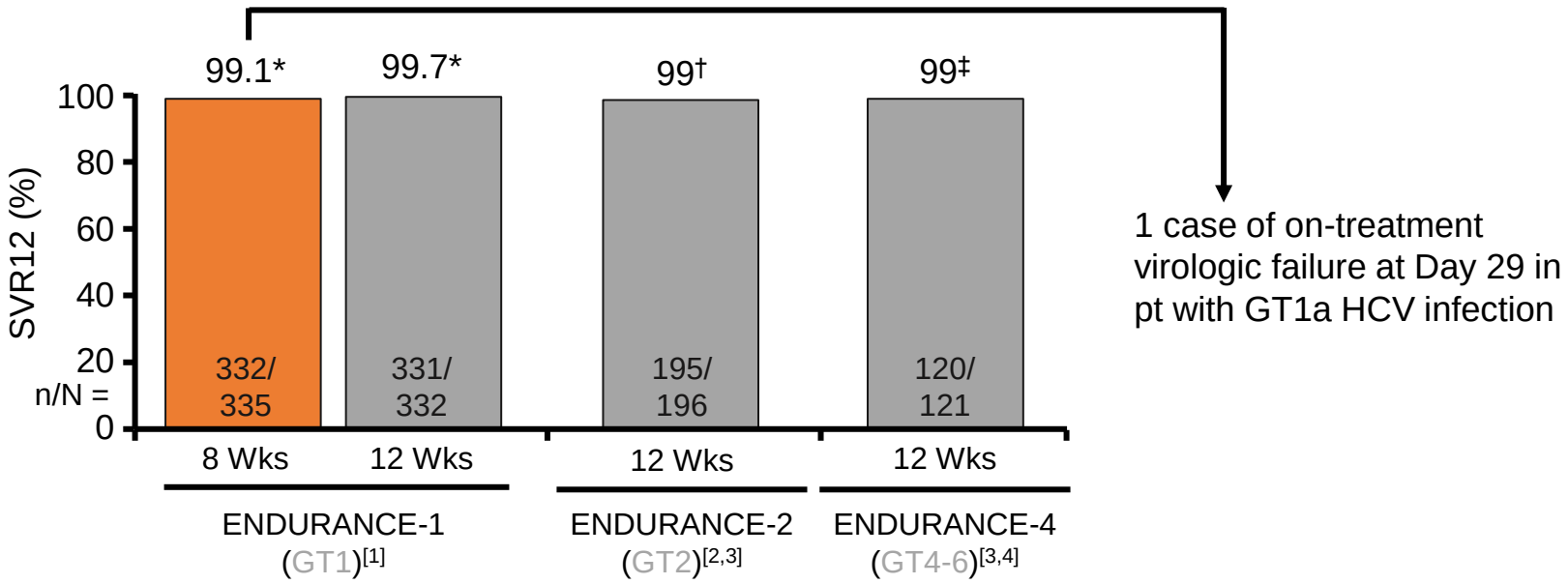
HCV-TARGET: Real-World Efficacy and Safety of SOF/VEL for GT1-6 HCV

- Pts treated per local standard of care at academic (n = 45) and community medical centers (n = 19) in North America (n = 60) and Europe (n = 4)
  - N = 451 for SOF/VEL; N = 119 for SOF/VEL + RBV



Landis CS, et al. AASLD 2017. Abstract 1096.

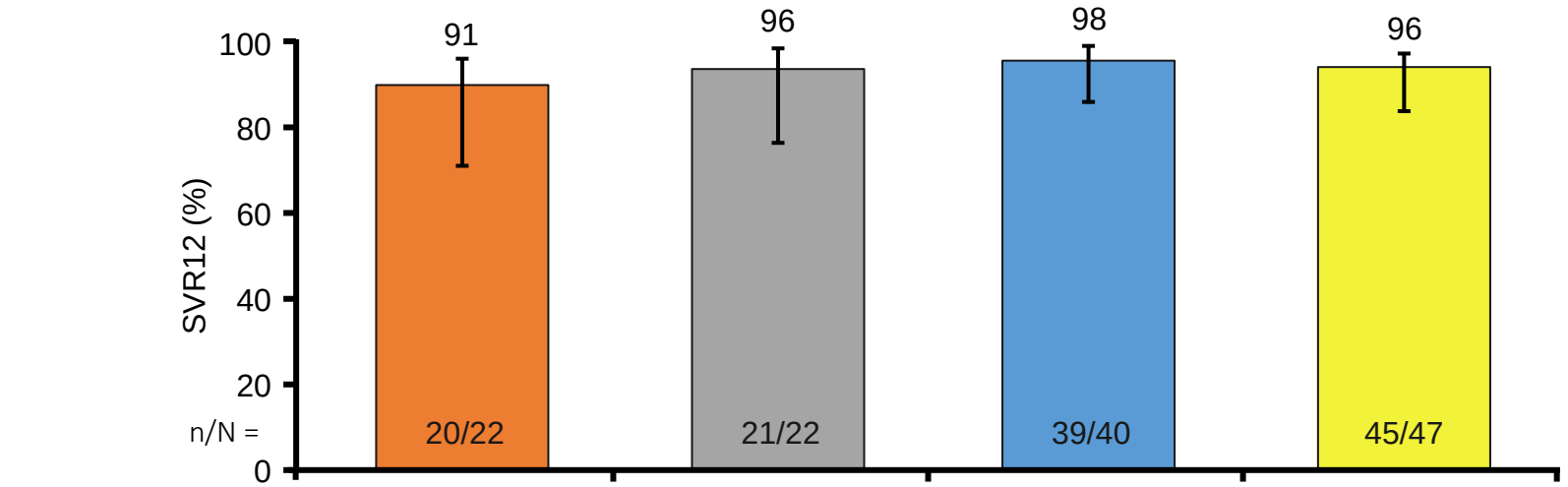
ENDURANCE-1, -2, -4 Studies: Efficacy of GLE/PIB for Treating GT1, 2, 4, 5, 6 HCV



*ITT-PS analysis: included all pts receiving ≥ 1 dose of study drug; excluded pts with HIV coinfection or SOF experience.
†ITT analysis: excluded pts with SOF experience. ‡ITT analysis.

1. Zeuzem S, et al. AASLD 2016. Abstract 253. 2. Kowdley KV, et al. AASLD 2016. Abstract 73. 3. Asselah T, et al. Clin Gastroenterol Hepatol. 2017;[Epub ahead of print]. 4. Asselah T, et al. AASLD 2016. Abstract 114.

SURVEYOR-II, Part 3: SVR12 Rates With GLE/PIB for Pts With GT3 HCV ± Cirrhosis

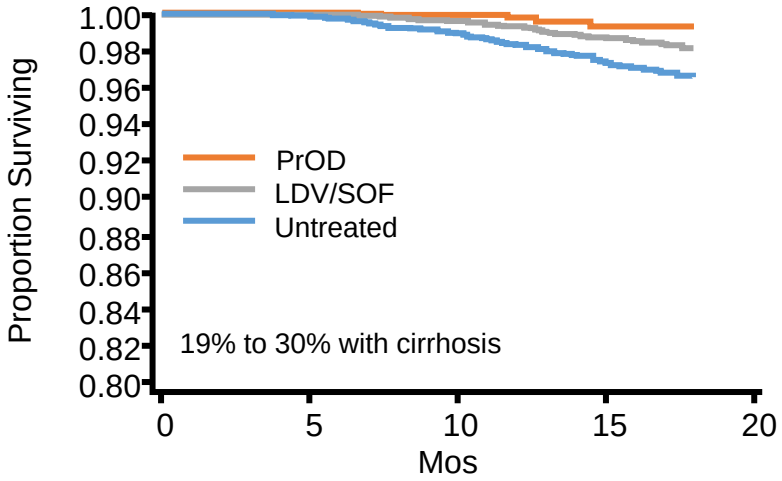


Tx Wks	12	16	12	16
Cirrhosis	-	-	+	+
Tx Experienced	+	+	-	+
Breakthrough	0	0	0	1
Relapse	2	1	0	1
LTFU	0	0	1	0

Wyles DL, et al. Hepatology. 2017;[Epub ahead of print].

Mortality Reduction Achieved by HCV Cure

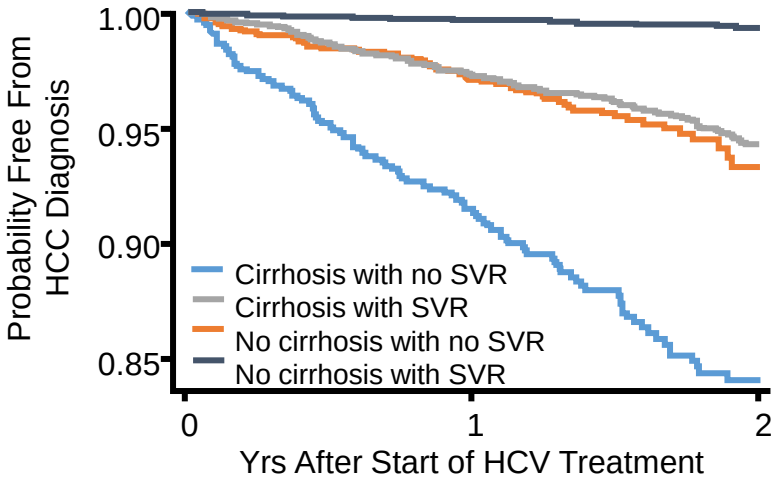
Survival in ERCHIVES Veterans (N = 13,940*†)[1]



DAA-induced SVR is associated with a 43% reduction in mortality

*For 18 mos of follow-up.
†BL cirrhosis: PrOD, 24.9%; LDV/SOF, 29.4%; untreated, 19.4%.

HCC Risk in DAA-Treated Veterans (n = 25,424‡)[2]

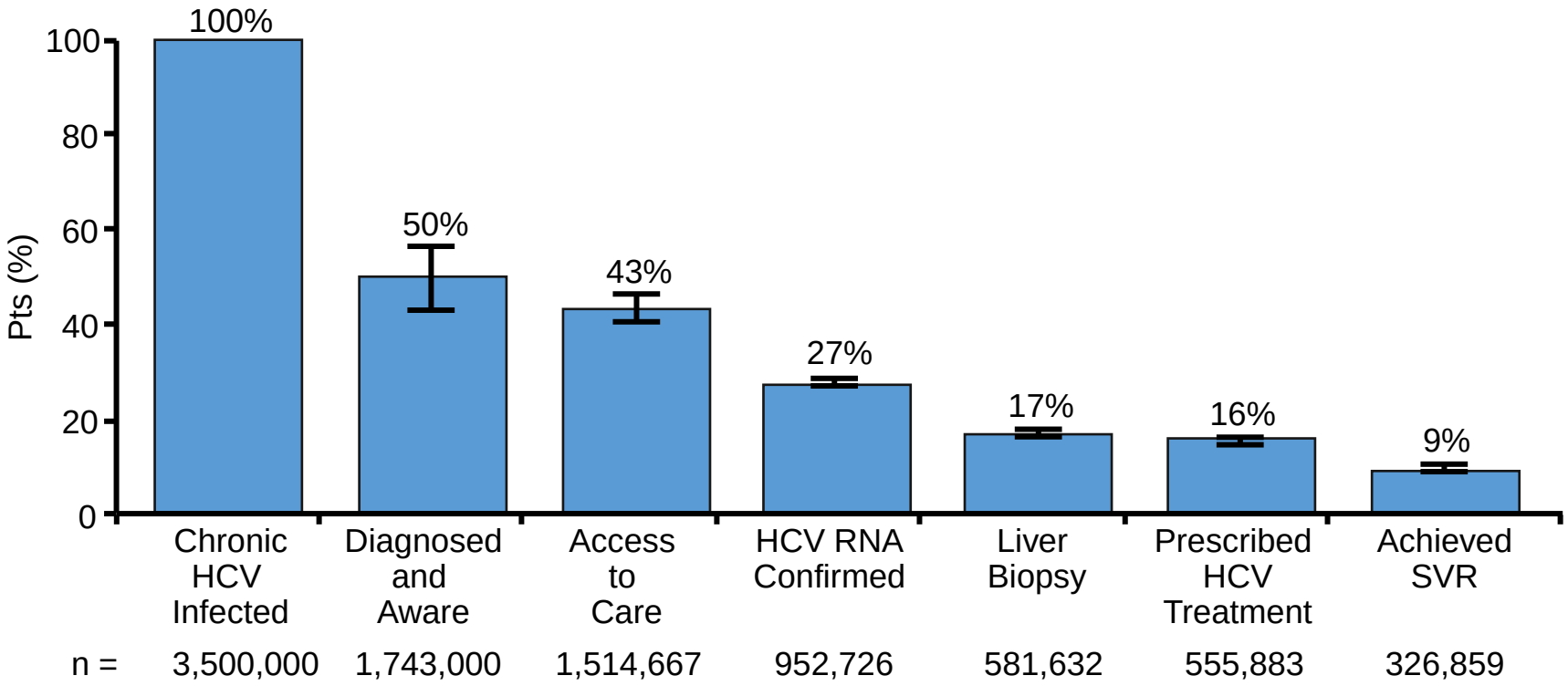


DAA-induced SVR is associated with a 71% reduction in HCC risk

‡For 38,204 pt-yrs of follow-up.

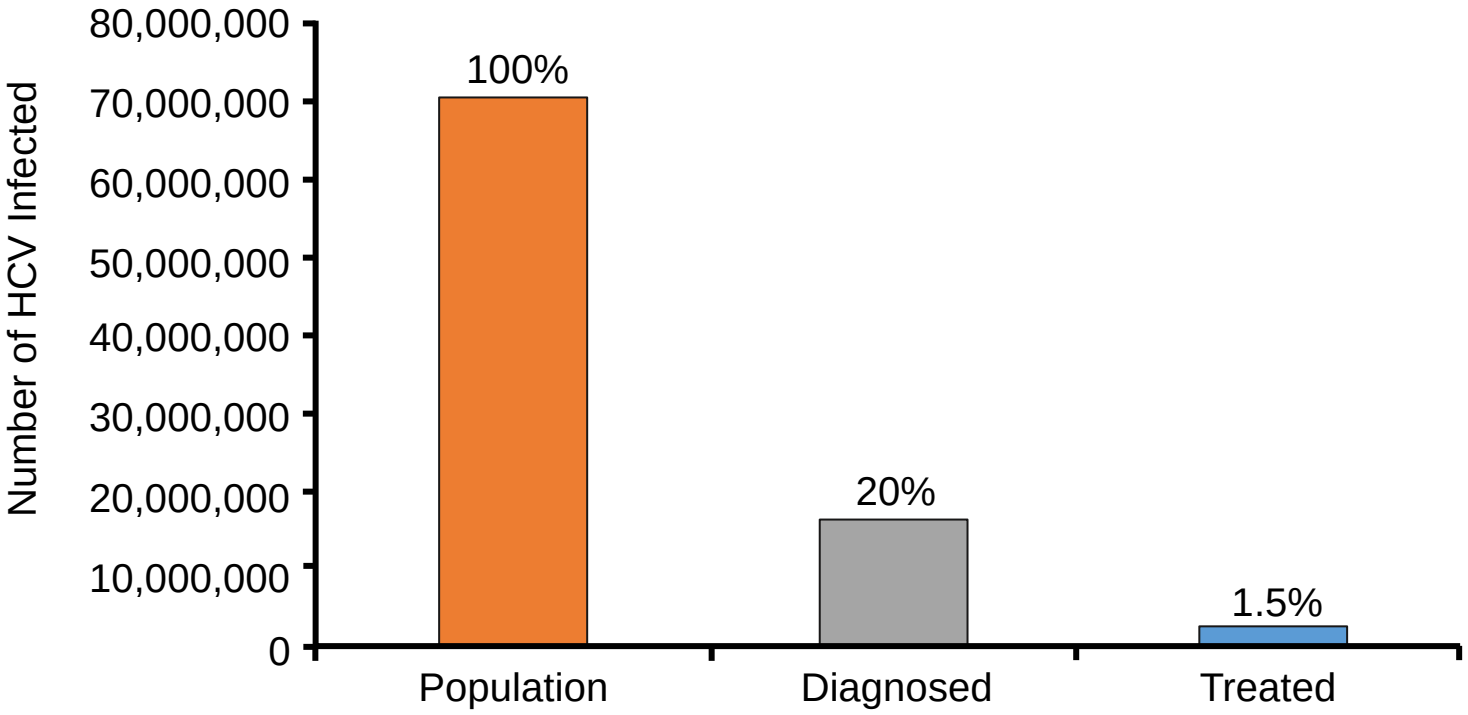
1. Butt AA, et al. Clin Infect Dis. 2017:65:1006-1011.
2. Ioannou GN, et al. J Hepatol. 2017;[Epub ahead of print].

In Practice Only a Small Proportion of HCV Patients Receive Treatment - the Cascade of Care



Yehia BR, et al. PLoS One. 2014;9:e101554.

Estimated Global HCV Cascade of Care



WHO 2015. http://www.who.int/mediacentre/factsheets/fs164/en/

Breakdowns in the HCV Care Cascade

High cost of HCV therapy leads to restrictions based on[1,2]:

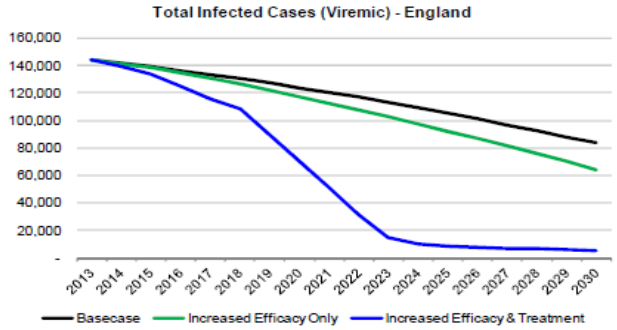
- Stage of disease
- Medical comorbidities
- Abstinence from drugs and alcohol
- Adherence concerns
- Insurance status

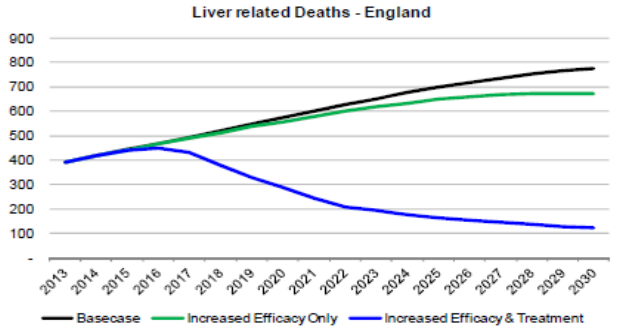
Populations with high HCV prevalence and variable access to healthcare[3]:

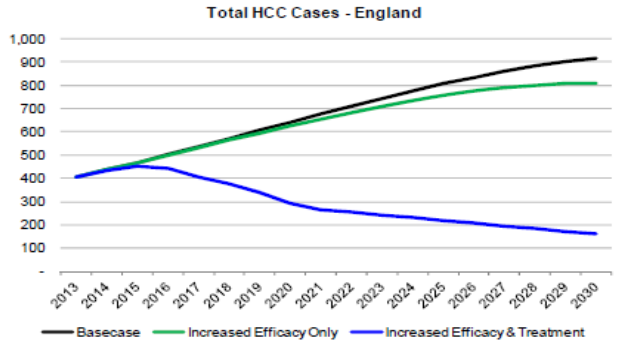
- Prisoners
- People living with HCV/HIV coinfection
- Men who have sex with men
- Migrants
- Persons who use drugs

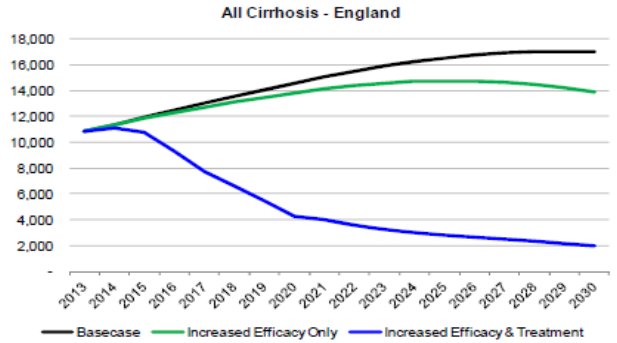
1. Yehia BR, et al. PLoS One. 2014;9:e101554. 2. Lynch SM, et al. J Clin Transl Hepatol. 2016;4:310-319. 3. Midgard H, et al. J Hepatol. 2016;65(1 suppl):S33-S45.

Impact of increasing testing and treatment of hepatitis C









	Base case	***2014***	***2016***	***2018***	***2030***
Eligibility	60%	60-80%	80%	95%	95%
Number treated	5430	8150	11,700	14,700	600
Stage of disease treated		>= F2	>=F1	any	any
Numbers newly diagnosed	5,600	6,700	10,000	15,100	880

Wedemeyer H et al J Viral Hepat. 2014

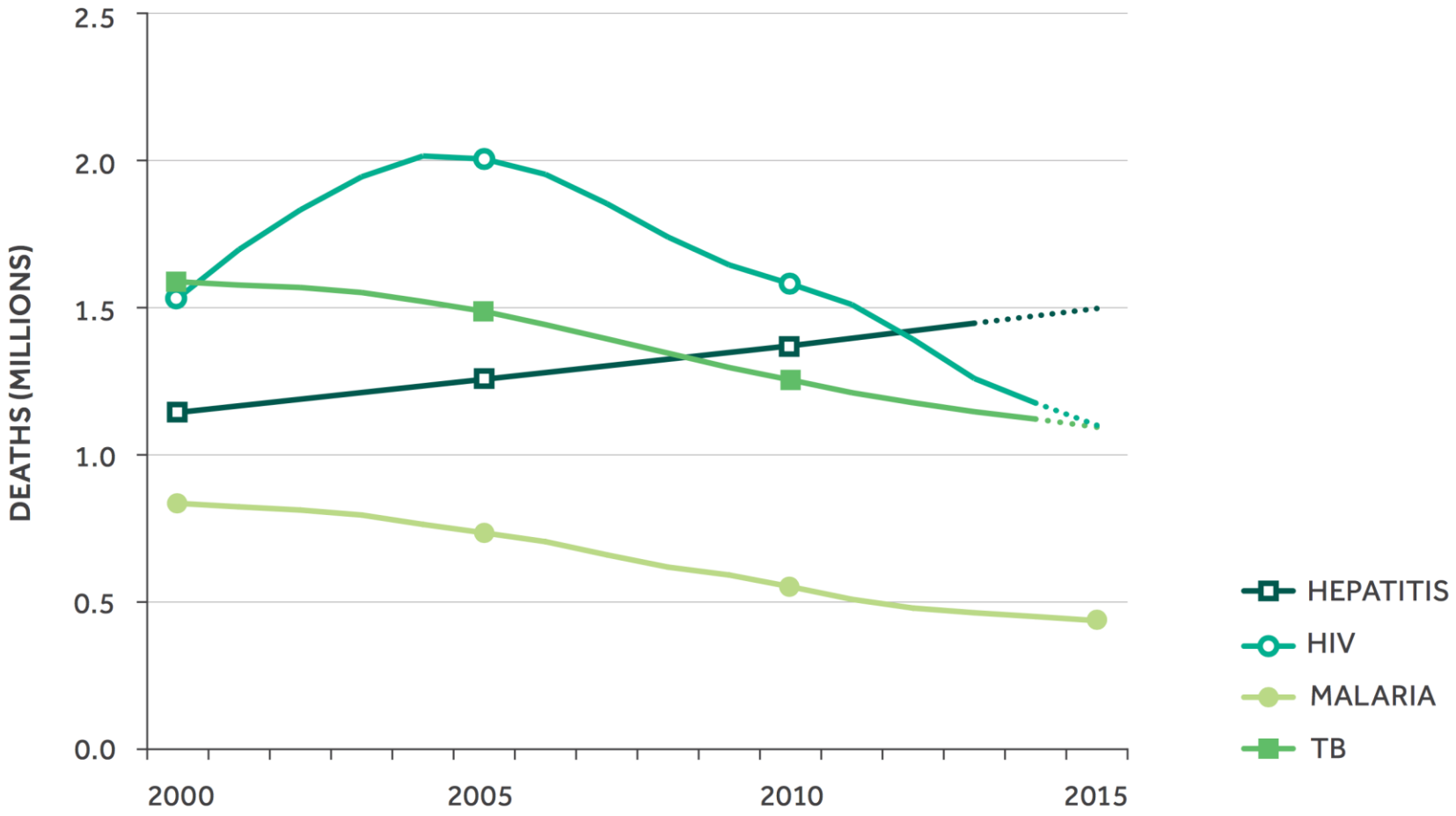
World Health Organization

JUNE 2016

GLOBAL HEALTH SECTOR STRATEGY ON VIRAL HEPATITIS 2016–2021

TOWARDS ENDING VIRAL HEPATITIS

Figure 2. Estimated global number of deaths due to viral hepatitis, HIV, malaria and TB, 2000–2015



Source: Global Burden of Disease and WHO/UNAIDS estimates, see http://ihmeuw.org/3pms, http://ihmeuw.org/3pmt (accessed 2 April 2016).

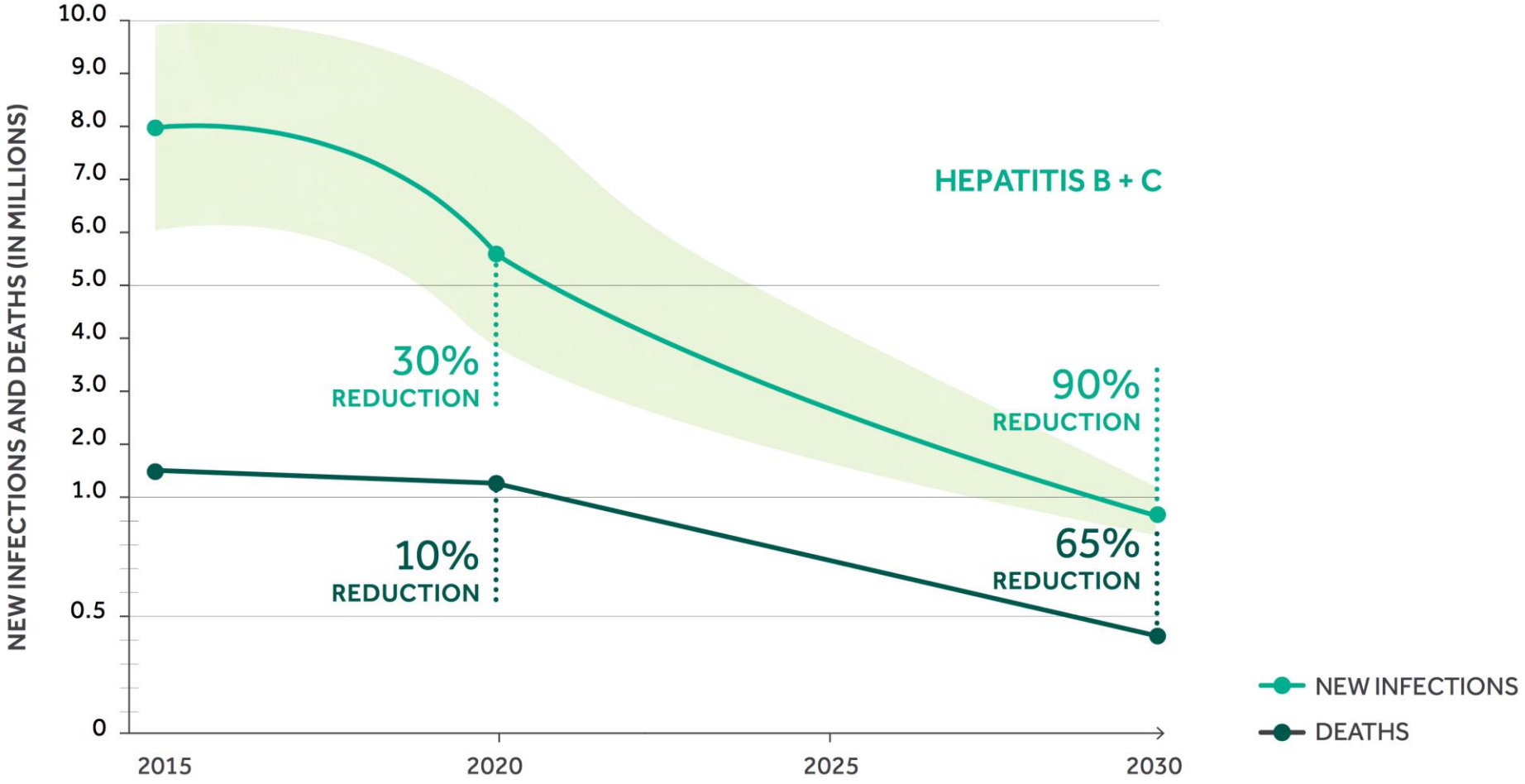
GLOBAL VISION

A world where viral hepatitis transmission is halted and everyone living with viral hepatitis has access to safe, affordable and effective prevention, care and treatment services.

GOAL

Eliminate viral hepatitis as a major public health threat by 2030.[8]

Figure 6. Targets for reducing new cases of and deaths from chronic viral hepatitis B and C infection



Service coverage targets	2015	2020	2030
Hepatitis B virus vaccination: childhood vaccine coverage (third dose coverage)	82%[11] in infants	90%	90%
Prevention of hepatitis B virus mother-to-child transmission: hepatitis B virus birth-dose vaccination coverage or other approach to prevent mother-to-child transmission	38%	50%	90%
Blood safety	39 countries do not routinely test all blood donations for transfusion-transmissible infections 89% of donations screened in a quality-assured manner[12]	95% of donations screened in a quality-assured manner	100% of donations are screened in a quality-assured manner
Safe injections: percentage of injections administered with safety-engineered devices in and out of health facilities	5%	50%	90%
Harm reduction: number of sterile needles and syringes provided per person who injects drugs per year	20	200	300
Viral hepatitis B and C diagnosis	<5% of chronic hepatitis infections diagnosed	30%	90%
Viral hepatitis B and C treatment	<1% receiving treatment	5 million people will be receiving hepatitis B virus treatment 3 million people have received hepatitis C virus treatment (Both targets are cumulative by 2020)	80% of eligible persons with chronic hepatitis B virus infection treated 80% of eligible persons with chronic hepatitis C virus infection treated

ADAPTING SERVICES

PRIORITY ACTIONS FOR COUNTRIES

Define populations and locations that are most affected and require intensified support, and prioritize them in the national hepatitis response while minimizing the risk of stigmatization.

Build community capacity to deliver quality community-based hepatitis services, supported by legal and regulatory frameworks and appropriate financial incentives.

Decentralize and expand hepatitis services to include, where appropriate, services in custodial settings, refugee camps and places of humanitarian concern.

Identify good models of integrated and linked service delivery through operational research, including linkages with other key health areas.

Improve the quality of services by setting national norms and standards for services, integrating quality indicators into strategic information systems and promoting the adoption and implementation of WHO guidelines.

Regularly undertake hepatitis "cascade analyses" for different populations and settings to determine the quality of services, assess service utilization and acceptability, identify major weaknesses and propose possible remedial actions.

HEP C ODNS AND CLINICAL LEADS

NHS England

North

1, North East & Cumbria
The Newcastle Upon Tyne Hospitals NHS Foundation Trust
Dr Stuart McPherson

2, Greater Manchester & Eastern Cheshire
Pennine Acute Hospitals NHS Trust & Central Manchester University Hospitals NHS Foundation Trust
Dr Andrew Ustianowski
Dr Martin Prince

3, Cheshire & Merseyside
Royal Liverpool & Broad Green University Hospital NHS Trust
Dr Paul Richardson
Professor Anna Maria Geretti

4, South Yorkshire
Sheffield Teaching Hospitals NHS Foundation Trust
Dr Ben Stone

5, Humberside and North Yorkshire
Hull & East Yorkshire NHS Trust
Dr Peter Moss

6, West Yorkshire
Leeds Teaching Hospitals
Dr Mark A Aldersley

7, Lancashire and South Cumbria (in development)

Midlands & East

8, Leicester
University Hospitals of Leicester
Dr Martin Wiselka

9, Birmingham
University Hospitals Birmingham NHS Foundation Trust
Professor David Mutimer

10, Nottingham
Nottingham University Hospitals NHS Trust
Dr Stephen Ryder

11, Eastern Hepatitis Network
Cambridge University Hospitals NHS Foundation Trust
Dr William Gelson

London North West

12, West London
Imperial College Healthcare Trust
Prof Mark Thursz

North Central London

13, North Central London
Viral Hepatitis Network
Royal Free London NHS Foundation Trust
Prof William Rosenberg

London North East

14, Barts
Barts Health (Royal London Site)
Prof Graham Foster

London South

15, South Thames Hepatitis Network (STHepNet) Kings & St George's
Kings College Hospital NHS Foundation Trust and St George's University Hospitals NHS Foundation Trust
Dr Kosh Agarwal
Dr Dan Forton

South

16, Surrey Hepatitis Services
Royal Surrey County Hospital NHS FT
Dr Michelle Gallagher

17, Sussex Hepatology Network
Brighton & Sussex University Hospitals – Royal Sussex County Hospital (RSCH)
Dr Jeremy Tibble

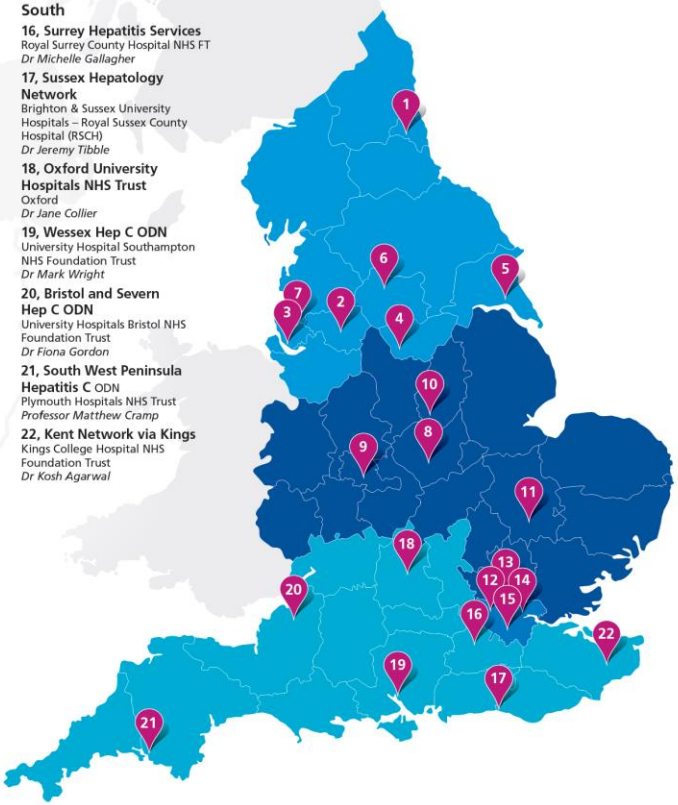
18, Oxford University Hospitals NHS Trust
Oxford
Dr Jane Collier

19, Wessex Hep C ODN
University Hospital Southampton NHS Foundation Trust
Dr Mark Wright

20, Bristol and Severn Hep C ODN
University Hospitals Bristol NHS Foundation Trust
Dr Fiona Gordon

21, South West Peninsula Hepatitis C ODN
Plymouth Hospitals NHS Trust
Professor Matthew Cramp

22, Kent Network via Kings
Kings College Hospital NHS Foundation Trust
Dr Kosh Agarwal



The NHS in England has introduced operational delivery networks (ODNs) for HCV treatment

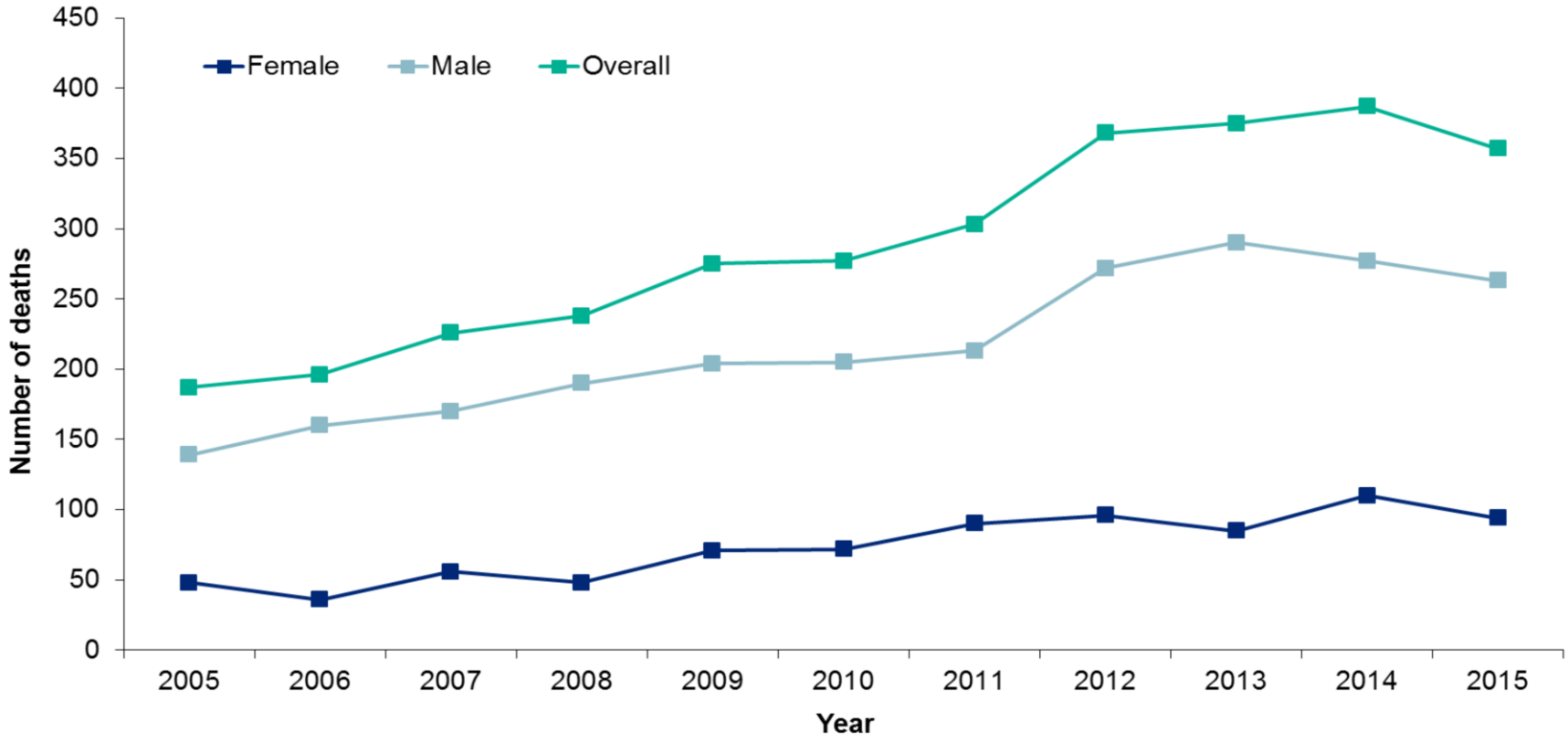
Operational Delivery Networks (ODNs) 3 phases:

1. 2014 - Early access treatment for patients with decompensated cirrhosis

2. 2015 - Access for patients with cirrhosis

3. 2016 - Treatment for all

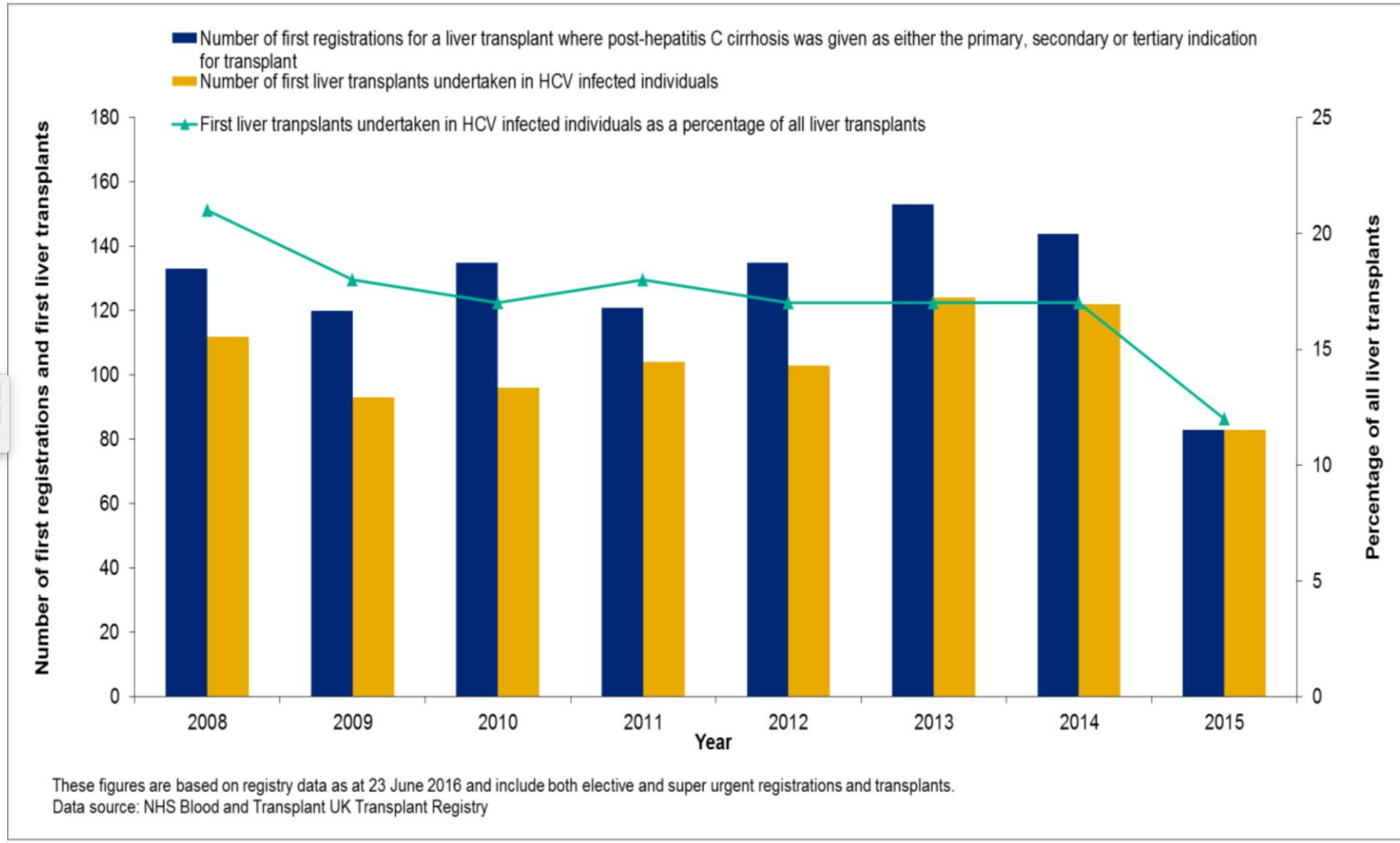
Figure 4. Deaths from ESLD* or HCC in those with HCV mentioned on their death certificate in England: 2005 to 2015



* Defined by codes or text entries for ascites, bleeding oesophageal varices, hepato-renal syndrome , hepatic encephalopathy or hepatic failure.
Data source: Office for National Statistics

Hepatitis C in England: 2017 report - PHE

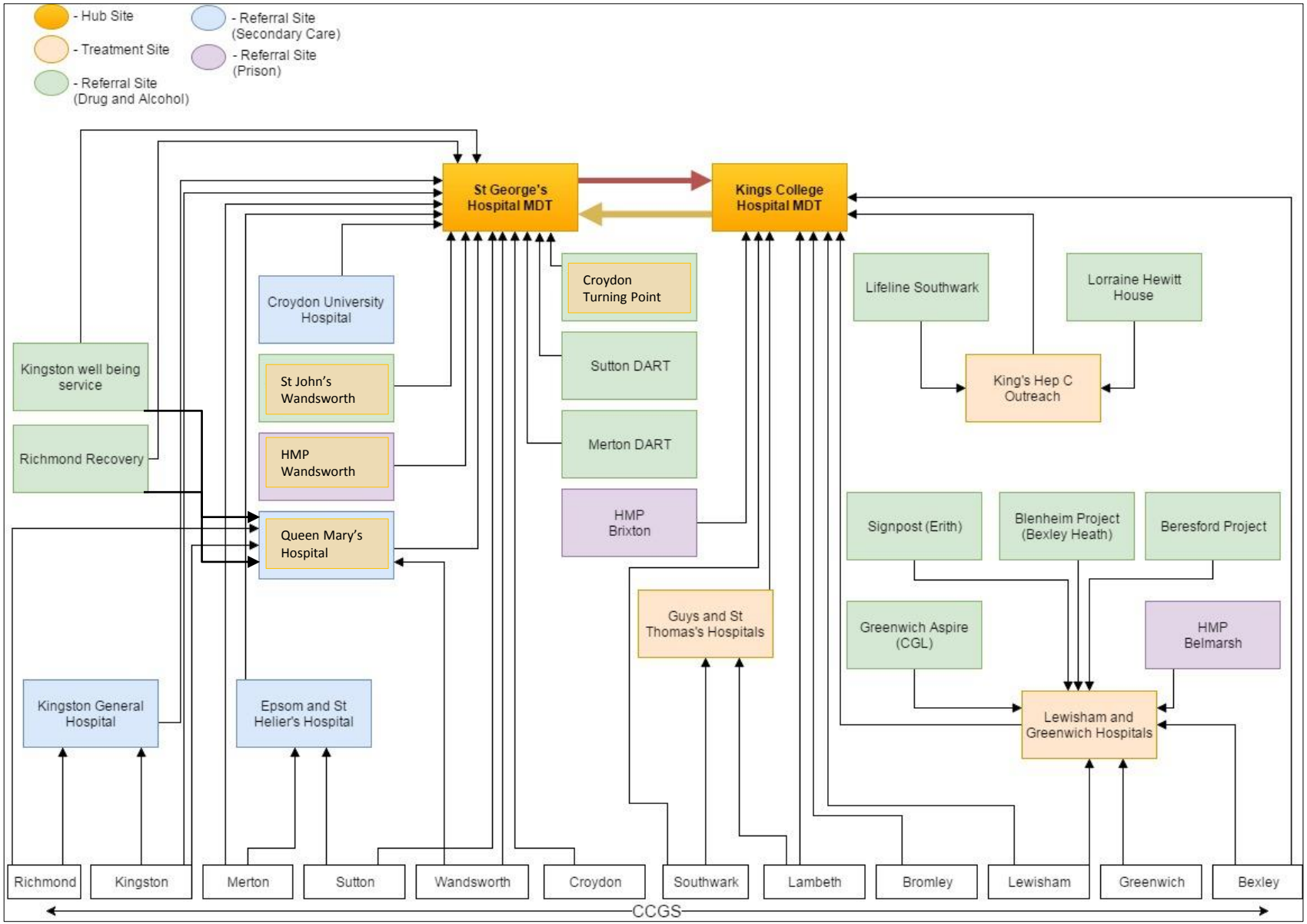
Figure 3. Number of first registrations and liver transplants undertaken in England where post-hepatitis C cirrhosis was given as either the primary, secondary or tertiary indication for transplant: 2008 to 2015



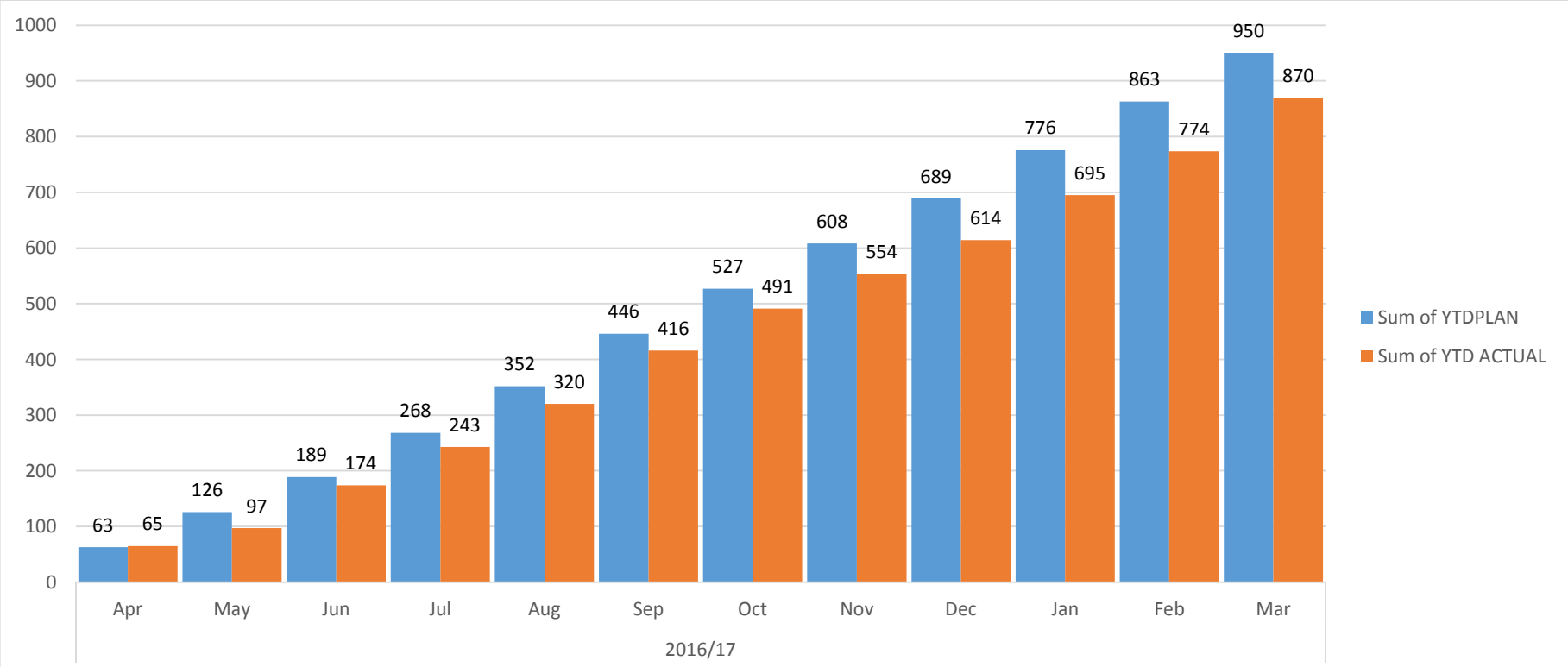
These figures are based on registry data as at 23 June 2016 and include both elective and super urgent registrations and transplants.
Data source: NHS Blood and Transplant UK Transplant Registry

Hepatitis C in England: 2017 report - PHE

ODN Referral Pathway Map



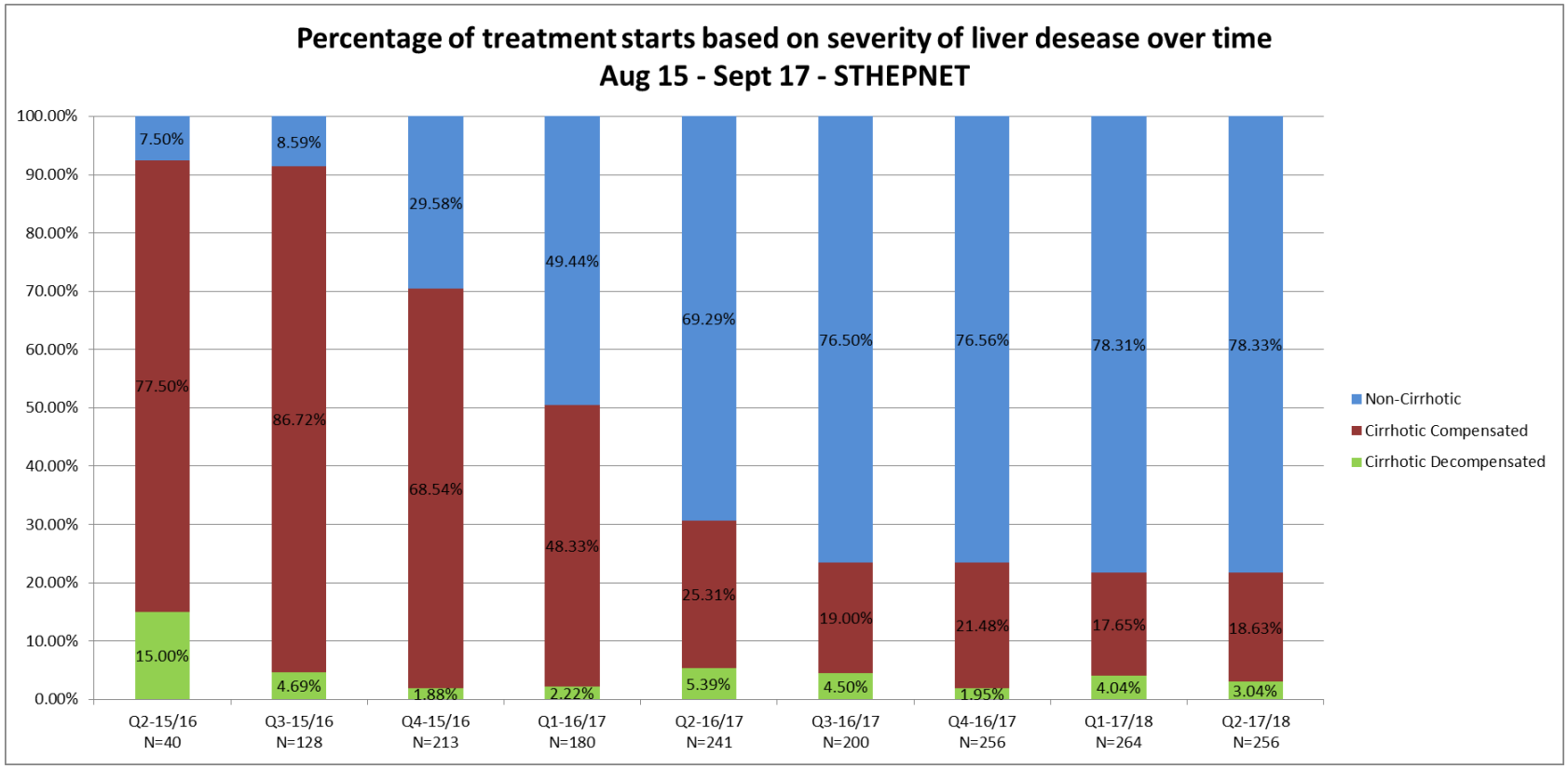
Total patients treated 16/17



Trust	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Totals
GUY'S AND ST THOMAS	12	1	15	6	18	10	7	13	12	14	4	17	129
KING'S COLLEGE HOSPITAL	23	7	33	36	32	47	45	28	27	39	41	37	395
LEWISHAM AND GREENWICH	7	4	6	7	14	8	2	9	10	7	8	8	90
ST GEORGE'S UNIVERSITY HOSPITALS	23	20	23	20	13	31	21	13	11	21	26	34	256
Grand Total	**65**	**32**	**77**	**69**	**77**	**96**	**75**	**63**	**60**	**81**	**79**	**96**	**870**

- 91.5% of prescribed run rate – End of year

Prioritisation of patients



STHepNet 5 year plan

Improving access to Hep C Treatment

- Education of high risk groups and key workers to promote testing and positive messages around treatment.
- Continued diagnostic innovation and provision of rapid-turnaround diagnostics in the community.
- Direct linkage from testing into community-based treatment.
- Provision of increased peer support.
- Appropriate infrastructure to treat the prison population.
- Case finding - HepCare

SWL outreach locations

- Queen Mary's Hospital, Roehampton - 2013
  - Consultant/CNS
  - Referrals from Kingston, Twickenham, Richmond, Wandsworth drug clinics
- St John's Therapy Centre, Clapham with Wandsworth CDAS – 2014
  - CNS
- Turning Point Croydon – 2017
  - Consultant/CNS/BBV nurse
- HMP Wandsworth – 2007
  - CNS/BBV nurse
- Nelson Hospital, Merton - 2017
  - CNS

Facilitating Outreach

- Proactive commissioning
- Enthusiastic, proactive drug services (staff, management, clients)
- Enthusiastic, non-judgemental providers
- Continuing education at every level
- Involvement of BBV staff and key workers in case management
- Enabling finance
- Enabling logistics – bloods, Fibroscan, pharmacy
- Novel diagnostics and monitoring – capillary blood
- Client confidence, peer referral

Capillary blood testing

- 100-500 microL
- HBV/HCV/HIV serology and HCV VL/genotype

Opt-out testing at HMP Wandsworth

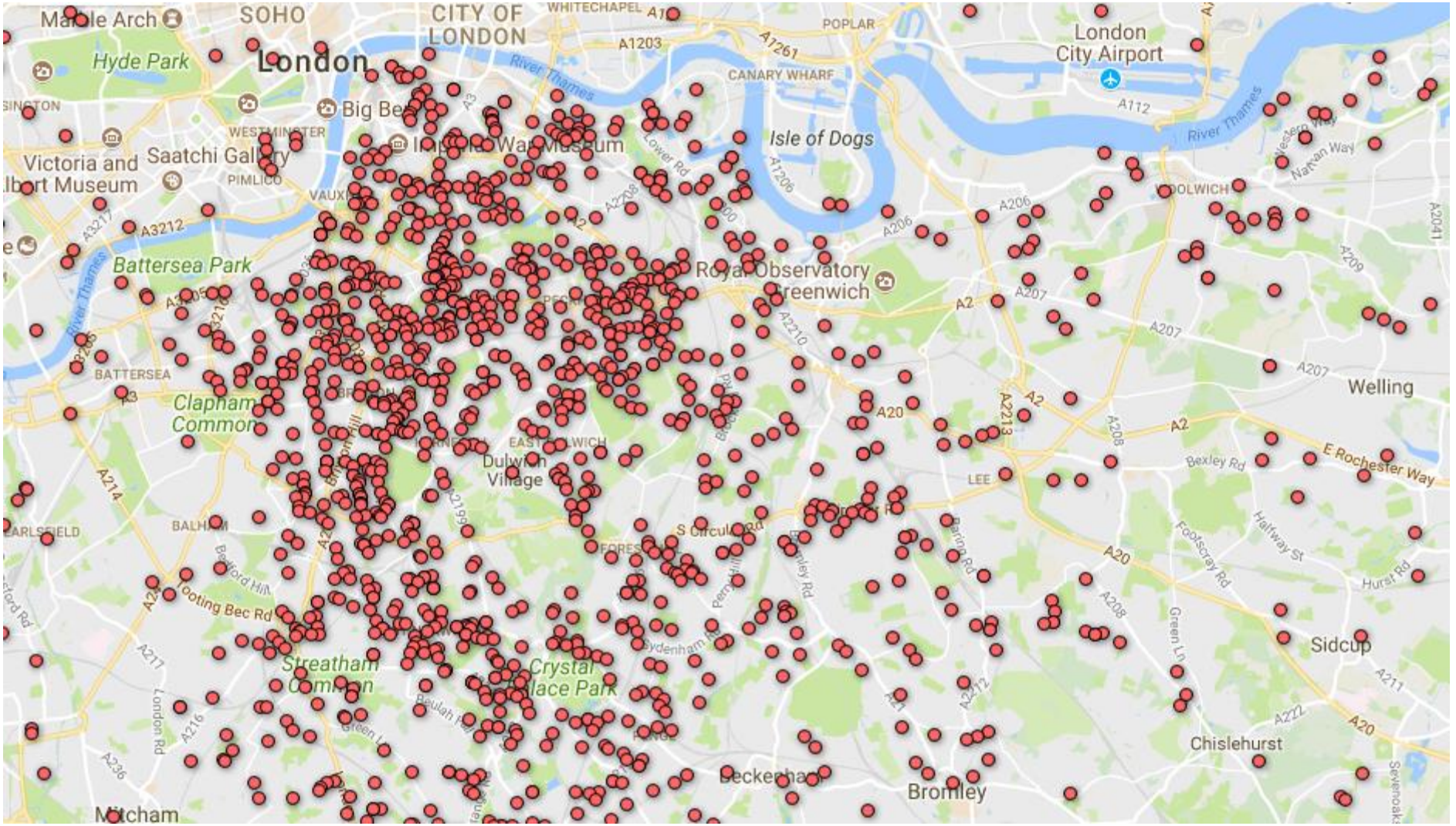
Stage	April	May	June	July	Aug
Total new receptions	428	601	542	449	529
Number offered test	339	491	392	364	399
Number tested	158	271	295	323	353
Number positive for HCV antibody (DBST)	15	18	27	21	19
Number offered blood test (for confirmation)	10	16	16	14	
Number RNA positive for HCV	10	13	18	15	
Total number with previous diagnosis of HCV	6	6	9	8	

HepCARE

- Clinical Management Tool and Database for HBV/HCV
- Linked to SWL Pathology – captures all positive HBV/HCV results (historical and prospective) with "push" of associated pathology results
- Calculates fibrosis scores / uploads Fibroscan data
- Allows tracking of treatment response
- Linked to PHE HCV Registry for seamless upload
- Excellent case – finding tool

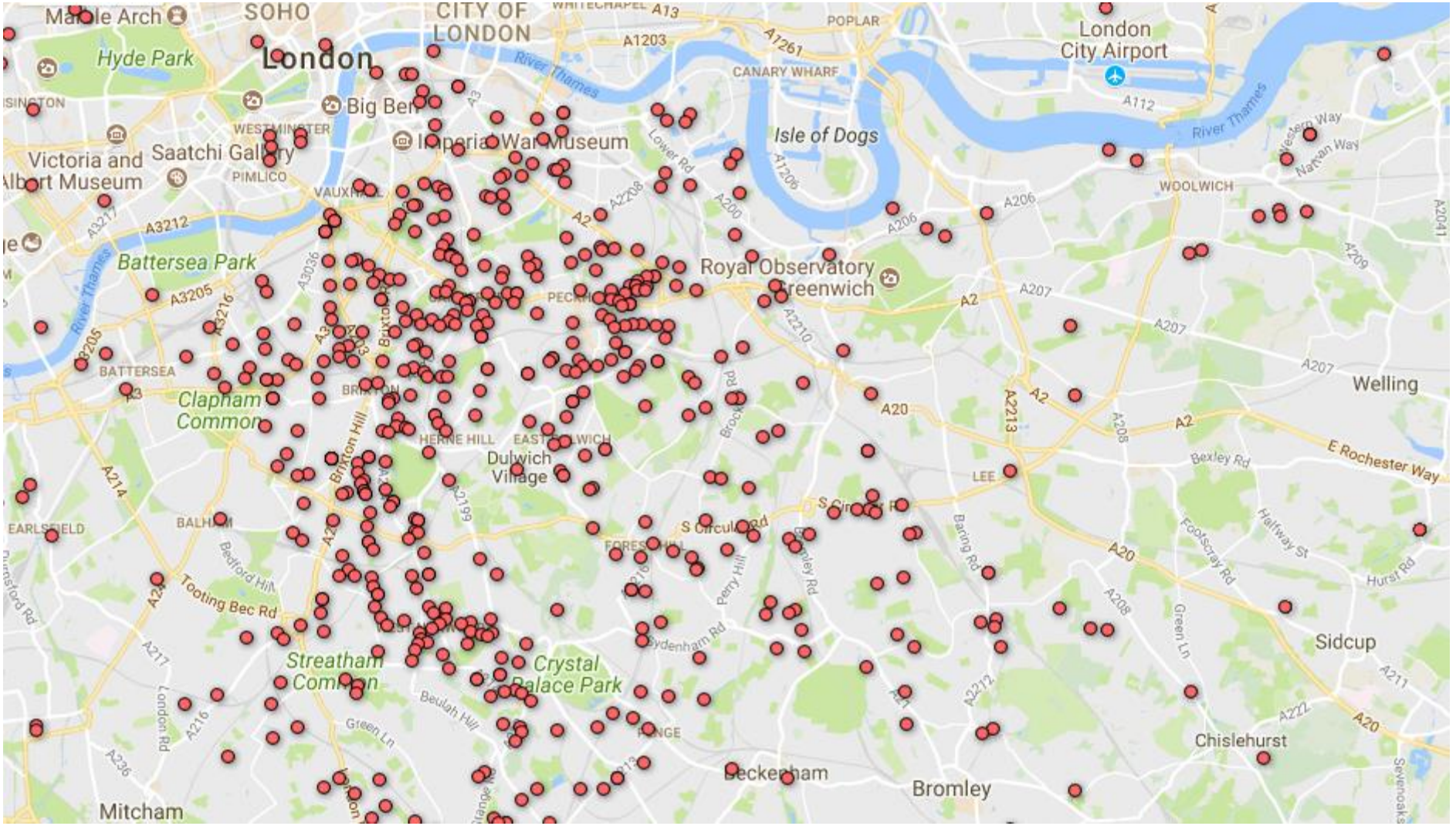
HepCARE Data examples

Patients RNA+ in last 5 years



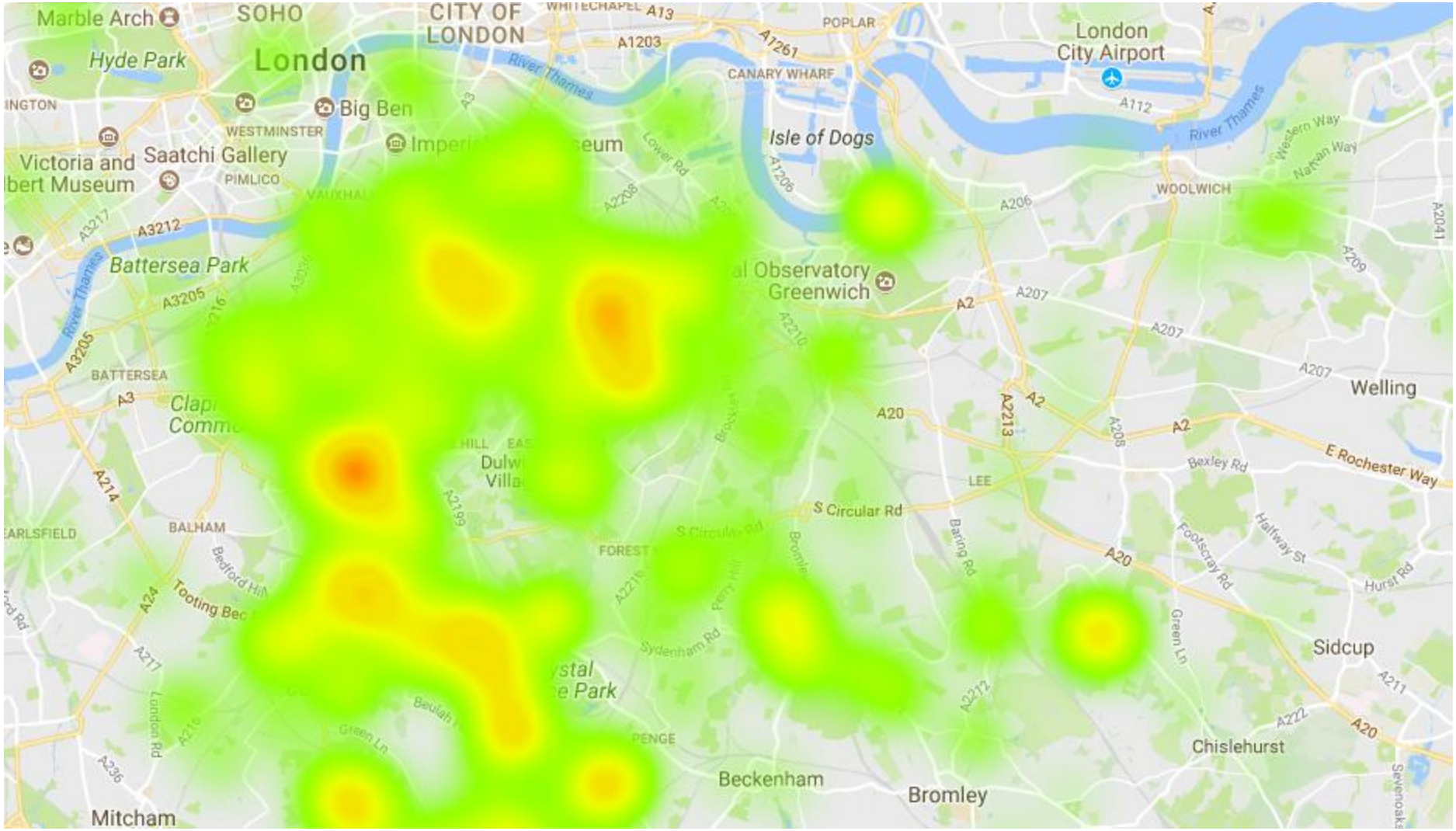
HepCARE Data examples

Patients RNA+ at last result



HepCARE Data examples

Patients RNA+ at last result, heatmap weighted to fibroscan (2.5-75Kpa)



NICE guidance for primary care

- Offer testing for hepatitis B and C to adults and children at increased risk of infection, particularly migrants from medium- or high-prevalence countries and people who inject or have injected drugs
- Offer testing for hepatitis B and C to people who are newly registered with the practice and belong to a group at increased risk of infection
- Ask newly registered adults if they have ever injected drugs, including image and performance enhancement substances at their first consultation.
- Offer annual testing for hepatitis C to people who test negative for hepatitis C but remain at increased risk of infection.
- Ensure people diagnosed with hepatitis B or C are referred to specialist care.

http://www.nice.org.uk/Guidance/ph43

Conclusions

- Unprecedented rapid progress from discovery to cure
- Paralleled progress in molecular science
- Testament to collaboration between academic research, pharmaceutical industry and clinicians
- We have moved from grappling with a complex problem in an individual to a complex problem in a population
- Unprecedented opportunity to eliminate HCV through treatment
- Achievement of WHO targets is a key global challenge