Hepatitis C:
Is Eradication Possible?

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2016: WHA Endorses Elimination of HCV as a Public Health Threat

- **WHO 2030 Targets:**
  - 90% diagnosed
  - 80% treated
  - 65% reduced mortality

WHO. Global health sector strategy on viral hepatitis 2016-2021. 2016.

HCV Meets Most Criteria for Elimination

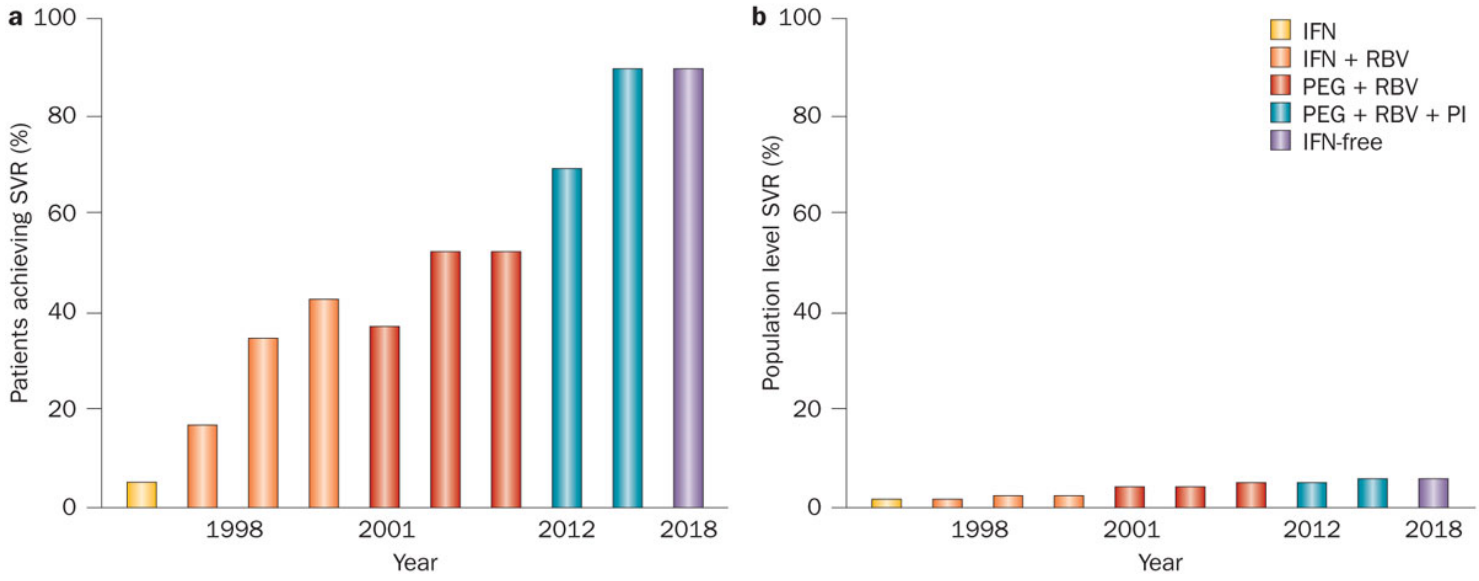
- No non-human reservoir
- Virus cannot amplify in the environment
- Practical interventions to interrupt transmission
- Infection is curable
- Can we do it without a vaccine?

Modified from: Edlin BR, Winkelstein ER. *Antiviral Res* 2014;110:79–93

Disparity Between Potential HCV Treatment Efficacy and Projected HCV Treatment Effectiveness

SVR in individuals

SVR in the population



Lack of expanded testing will have no impact on unrecognized HCV infection

Modified from Thomas, D. L. *et al. Lancet* 2010;376:1441–1442

Net Change in Epidemic Size Between 2016 and 2017

Net cure rate: N. achieving SVR – new HCV infections + HCV-related deaths

Region	HCV Epidemic 2016	New HCV infections	Number cured	HCV-related deaths	HCV Epidemic 2017	Net change
Asia and Pacific	29,564,900	574,330	456,552	179,810	29,502,868	–62,032
Central and Eastern Europe	6,507,700	322,800	26,110	15,505	6,788,885	+281,185
Latin and South America	3,477,400	27,537	47,859	21,496	3,435,582	–40,548
North Africa and Middle East	7,399,470	156,660	542,724	51,944	6,961,462	–438,008
North America	2,955,600	31,870	216,731	20,829	2,749,910	–205,690
Sub-Saharan Africa	5,069,000	130,800	3,805	21,540	5,174,455	+105,455
Western Europe	2,364,430	35,440	105,821	14,951	2,279,098	–85,332
91 country subtotal	57,338,500	1,279,437	1,399,602	326,075	56,892,260	–446,240
Missing countries	12,216,308	318,375	113,157	57,923	12,363,603	+147,295
Global estimate	69,554,808	1,597,812	1,512,759	383,998	69,255,863	–298,945

– 0.4%

Hill A M et al. *J Virus Eradication* 2017; 3: 117–123

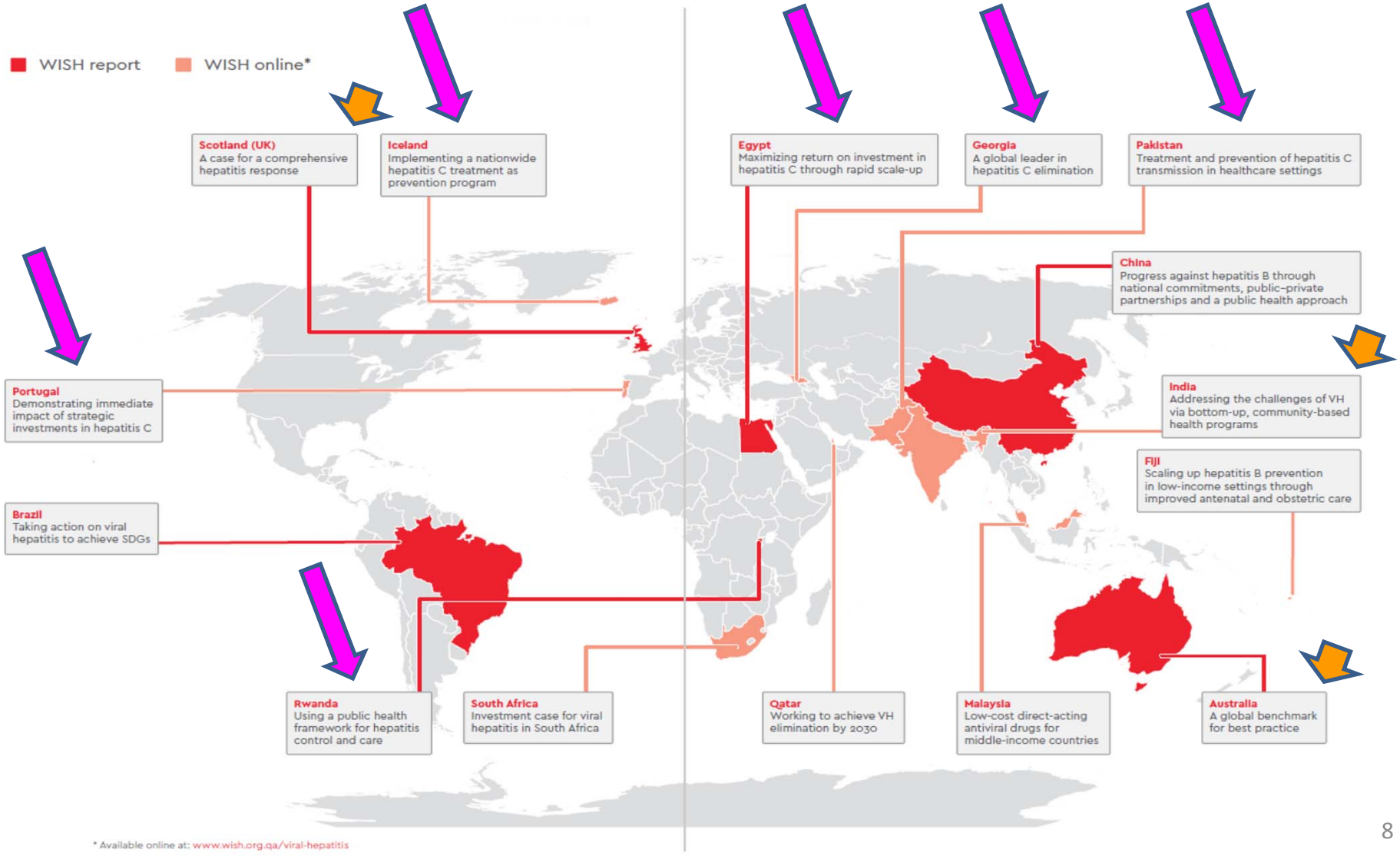
Treatment as Prevention Will Help Reaching WHO Targets by 2030 in Some but not All Countries

Challenges to HCV Elimination

- **Success Likely:**
  - Small countries
  - Promoting awareness
  - Large politically-supported advocacy and screening effort
  - Diagnosis linked to care
  - Identifiable risk cohorts
  - Financially sustainable
  - Access to generics
  - Wide-scale prevention programmes

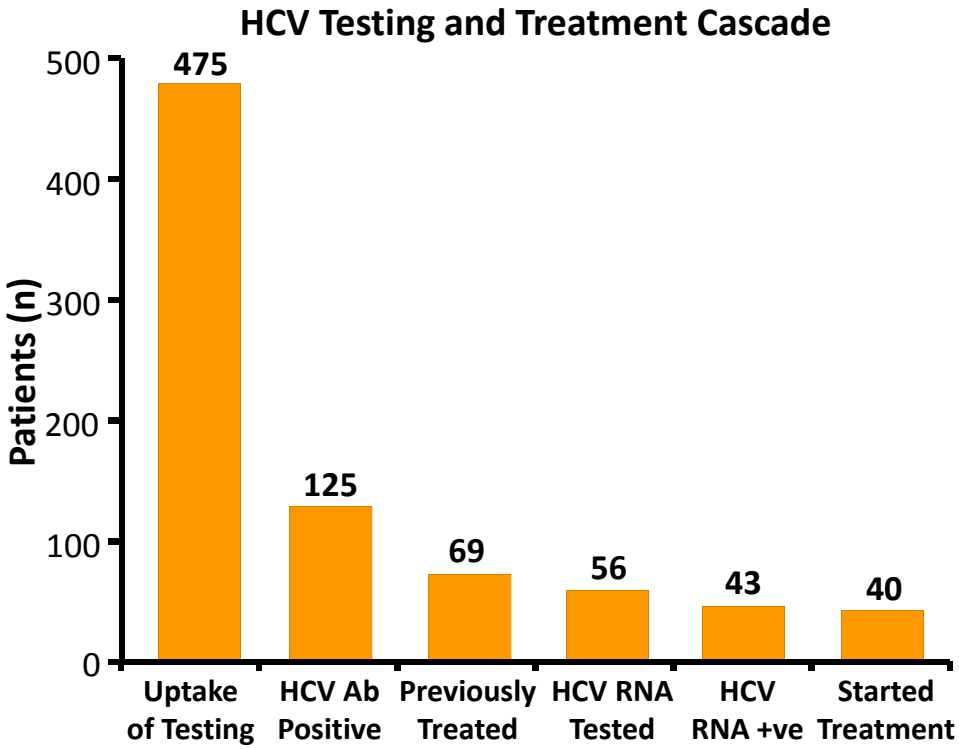
- **Success Unlikely:**
  - Large countries
  - No promotion of awareness
  - No active case finding
  - No direct linkage to care
  - No clearly identifiable risk cohorts
  - Doubtful financial sustainability
  - Limited or no access to generics
  - Treatment prioritization

Many Countries Are Implementing Effective Viral Hepatitis Strategies



Test-and-Treat Pilot: HCV

- **Screened for HCV Ab:** N = 475
- **HCV Ab positive:** 125/475 (26%), of whom 69 were previously treated, 56 were new cases
  - All 56 new cases assessed for HCV RNA
- **HCV RNA positive:** 43/56 (77%)
  - Prescribed HCV treatment with SOF 400 mg + DCV 60 mg: 40/43 (93%)
  - Not prescribed HCV treatment owing to focal hepatitis lesions, n = 2 (5%); pregnancy, n = 1 (2%)
- **Time from screening to treatment:** 3 h



Shiha. EASL 2019. Abstr PS-069. Reproduced with permission.

New Virological Tools Help Linkage to Care

- **“Classical” tools**
  - HCV core antigen (cAg)

- **Alternative tests (POCT)**
  - Rapid diagnostic tests (RDT)
  - Molecular POCT

- **Dried blood spot (DSB) for blood collection**

Problems in the Generation of Traditional HCV Vaccines

- Genetic variability:
  - Antibodies may recognize single variants within the viral quasispecies and unable to be broadly neutralizing
  - Hypervariable regions
- Virus-specific CD8+ T cells are generally not elicited by soluble immunogens
- Protein conformational variability
- Virus replication outpaces generation of immunity
- Lack of protective immunity

Sterilizing Immunity Is a Challenging Endpoint for Preventive HCV Vaccines

Neutralizing Abs are poorly effective and are generated also in chronic infection

HCV Vaccine: HCV-I gpE1/gpE2 Vaccination Followed by Heterologous Challenge in the Chimpanzee Model

Heterologous HCV-H challenge

	#	Dose	Number that developed: NO infection	Acute infection	Acute→Chronic infection
Vaccinees	3	64 CID_{50}	0	3	1
	1	10 CID_{50}	0	1	0
	1	10 CID_{50}	0	1	0
	4	100 CID_{50}	0	4	0
Total	9		0 (0%)	9 (100%)	1 (11%)
Controls	2	64 CID_{50}	0	2	1
	1	10 CID_{50}	0	1	1
	5	64 CID_{50}	0	5	5
	1	6.4 CID_{50}	0	1	0
	5	100 CID_{50}	0	5	1
Total	14		0 (0%)	14 (100%)	8 (57%)

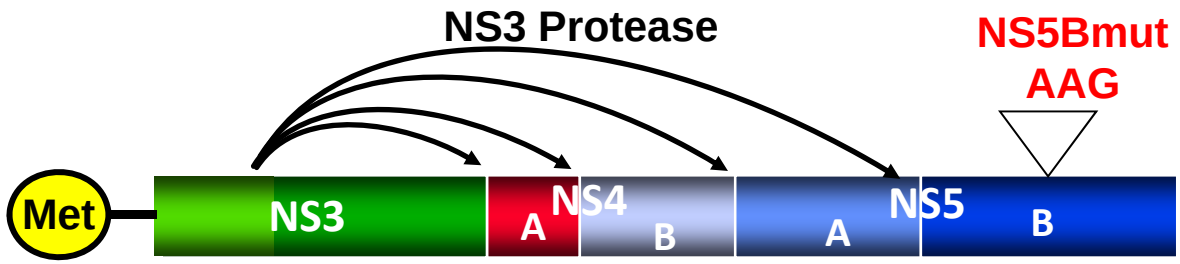
P = 0.040

Courtesy of Michael Houghton. Chiron Co., data on file

The Vaccine

Immunogen

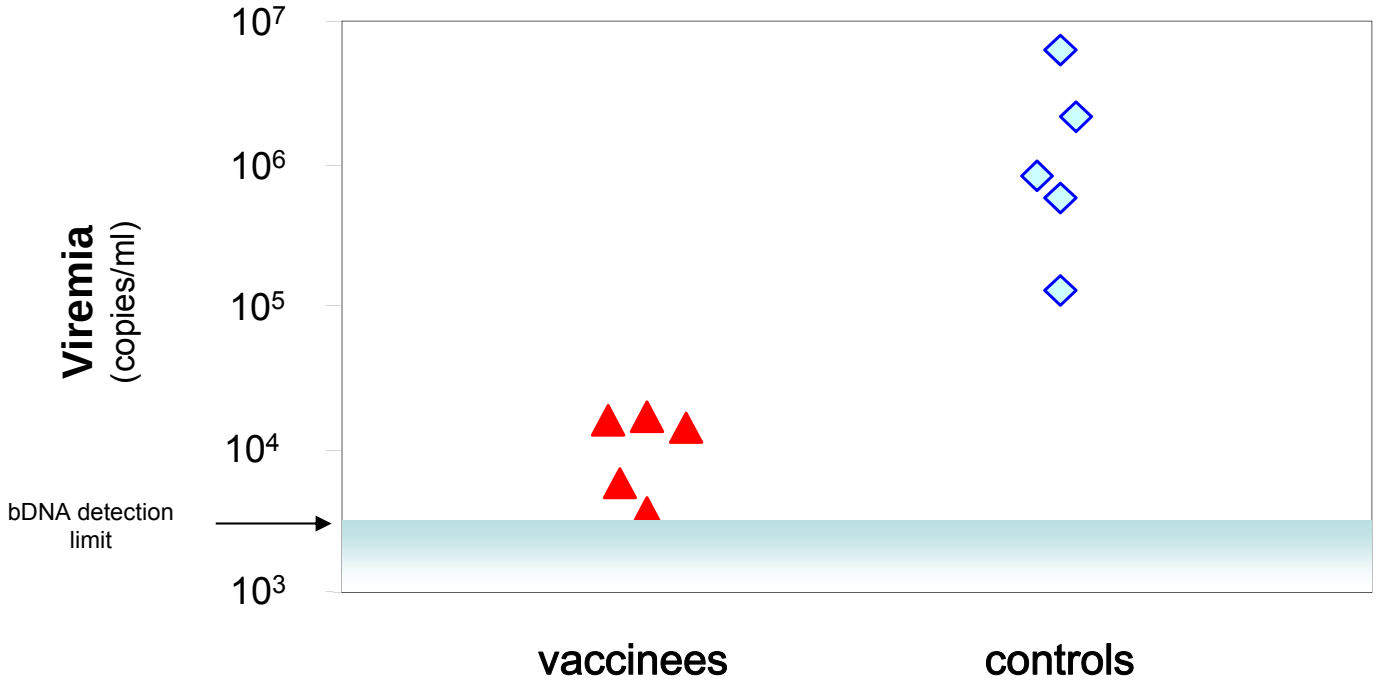
- NS3-NS5B (NS = 1985 aa)
- Genotype I, subtype 1b
- Most conserved HCV region
- Several epitopes



Prime-boost vaccination strategy based on a replicative defective simian adenoviral vector (ChAd3) and modified vaccinia Ankara (MVA) vector encoding the NS3, NS4, NS5A, and NS5B

Folgori, *Nat Medicine*, 2006

Vaccine Prevents Development of High Level Viremia in Chimps

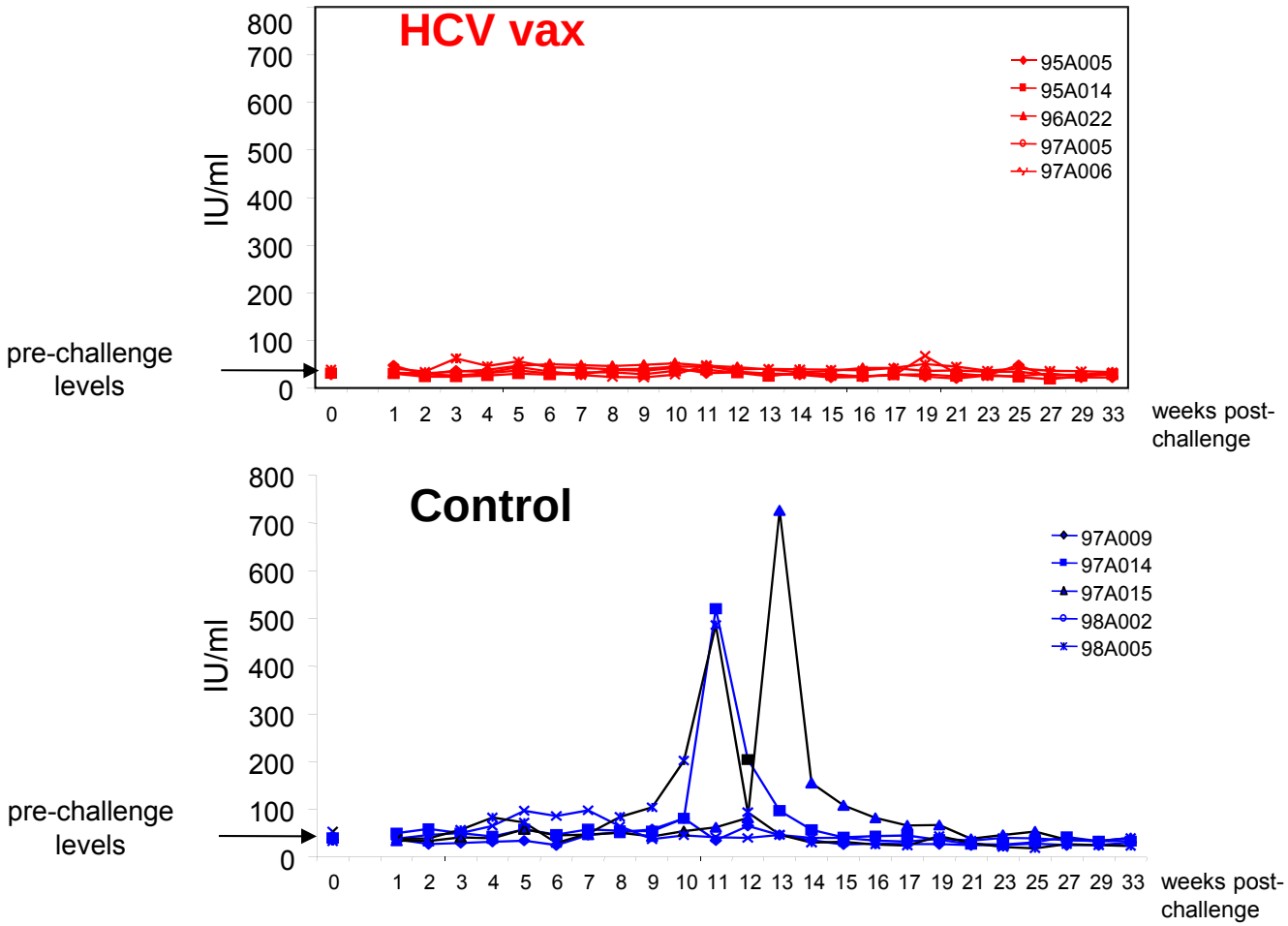


- More than 100 fold reduced viremia in the Vaccine group
  (p=0.009 by Mann Whytney)

Folgori, *Nat Medicine*, 2006

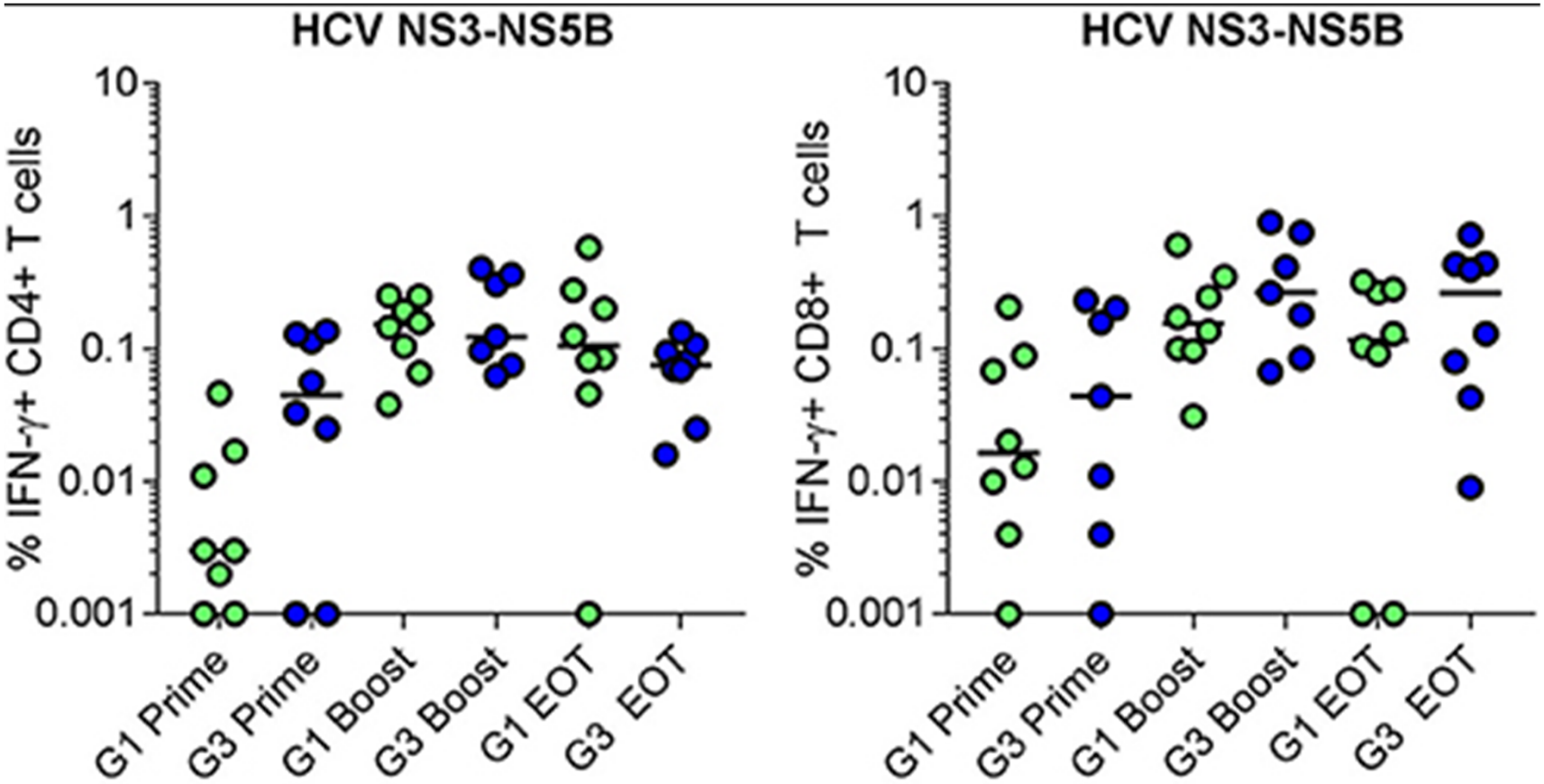
Vaccine Protects from Hepatitis

Assay: serum ALT



Folgori, *Nat Medicine*, 2006

Broad and Durable Ag-Specific IFN-γ+ CD4+ and CD8+ T Cells in Volunteers



Hartnell F, et al. *Front Immunol* 2019 Jan 18;9:3175.

Vaccine Now Being Tested for Protection Against Virus Persistence in HCV-Naïve PWID

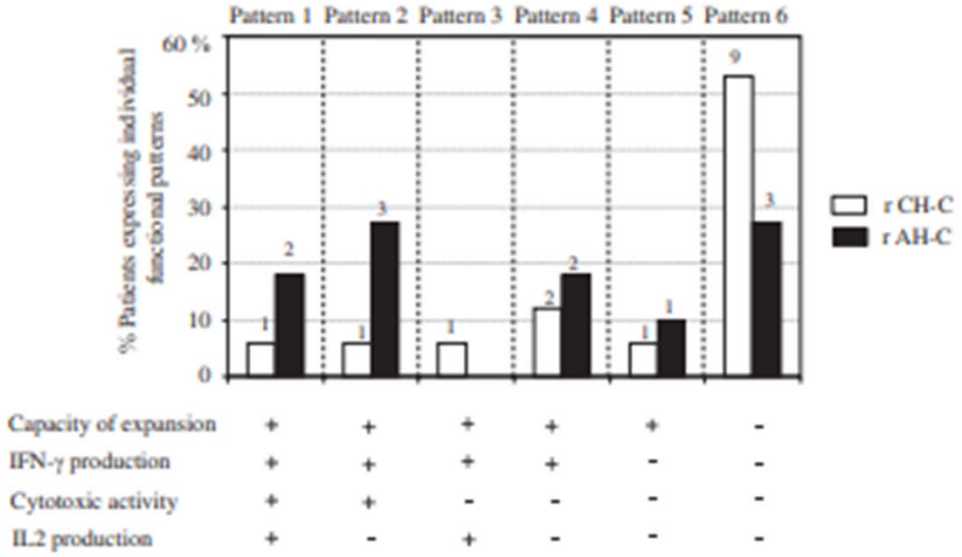
clinicaltrials.gov NCT01436357

- 1st hepatitis C vaccine efficacy trial in humans.
- Chimp adenoviral and MVA vectors to prime, boost, and sustain functional hepatitis C–specific T-cell memory (Sci Transl Med. 2014;6:261ra153).
- AdCh3NSmut–MVANSmut combination induced antiviral immunity, with broad and durable polyfunctional CD4 and CD8 T-cell responses across hepatitis C genotypes.
- AdCh3NSmut1–MVANSMut hepatitis C vaccine now being tested in a two-stage, phase 1/2, double-blind, randomized, placebo-controlled clinical trial involving 500 at-risk uninfected PWID volunteers followed for 18 months.
- Results expected in June 2019.

Lack of full CD8 functional restoration after antiviral treatment for acute and chronic hepatitis C virus infection

Gabriele Missale,[1] Massimo Pilli,[1] Alessandro Zerbini,[2] Amalia Penna,[1] Lara Ravanetti,[1] Valeria Barili,[1] Alessandra Orlandini,[1] Atim Molinari,[1] Massimo Fasano,[3] Teresa Santantonio,[4] Carlo Ferrari[1]

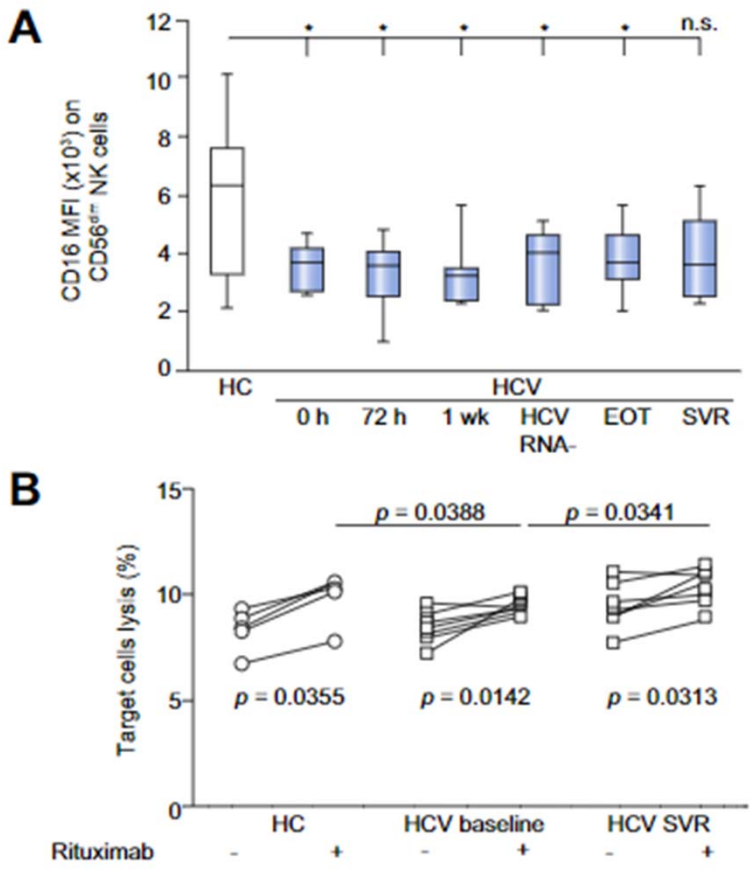
Gut 2012;**61**:1076–1084. doi:10.1136/gutjnl-2011-300515



Hepatitis C virus-induced NK cell activation causes metzincin-mediated CD16 cleavage and impaired antibody-dependent cytotoxicity

Barbara Oliviero[1,†], Stefania Mantovani[1,†], Stefania Varchetta[1], Dalila Mele[1], Giulia Grossi[1], Serena Ludovisi[1,‡], Elisa Nuti[3], Armando Rossello[3], Mario U. Mondelli[1,2,*]

J Hepatol 2017 Jun;66:1130-1137. doi: 10.1016/j.jhep.2017.01.032.



The Road to Elimination of Hepatitis C

- HCV can only be eliminated if annual rates of SVR are higher than new infections.
- **An annual net cure rate of 7%** is recommended to reach the WHO targets for elimination of HCV by 2030
- WHO goals can be achieved only in a minority of countries
- Eradication is not attainable without a vaccine
- Vaccine trials are difficult to organize. Experimental HCV infection in volunteers poses serious ethical considerations and may leave pervasive immunological defects.