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

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?

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

### Net Change in Epidemic Size Between 2016 and 2017

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

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

Net change: −0.4%
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

*Available online at: www.wish.org.cn/viral-hepatitis*
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

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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**

<table>
<thead>
<tr>
<th></th>
<th>Dose</th>
<th>No infection</th>
<th>Acute infection</th>
<th>Acute → Chronic infection</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccinees</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3</td>
<td>64 CID$_{50}$</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>10 CID$_{50}$</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>10 CID$_{50}$</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>100 CID$_{50}$</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>9</td>
<td>0 (0%)</td>
<td>9 (100%)</td>
<td>1 (11%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
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<th>Acute infection</th>
<th>Acute → Chronic infection</th>
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<tbody>
<tr>
<td><strong>Controls</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>64 CID$_{50}$</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>1</td>
<td>10 CID$_{50}$</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>64 CID$_{50}$</td>
<td>0</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>1</td>
<td>6.4 CID$_{50}$</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>100 CID$_{50}$</td>
<td>0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>14</td>
<td>0 (0%)</td>
<td>14 (100%)</td>
<td>8 (57%)</td>
</tr>
</tbody>
</table>

**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

Vaccine Prevents Development of High Level Viremia in Chimps

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

**Vaccine Protects from Hepatitis**

**Assay:** serum ALT

![Graph showing HCV vax and Control levels over weeks post-challenge]

*Folgori, Nat Medicine, 2006*
Broad and Durable Ag-Specific IFN-γ+ CD4+ and CD8+ T Cells in Volunteers

Vaccine Now Being Tested for Protection Against Virus Persistence in HCV-Naïve PWID
clinicaltrials.gov NCT01436357

- 1st hepatitis C vaccine efficacy trial in humans.
- 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 Pili,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 Ferrari1


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

Barbara Oliviero1,1, Stefania Mantovani1,1, Stefania Varchetta1, Dalila Mele1, Giulia Grossi1, Serena Ludovisi1,2, Elisa Nuti3, Armando Rossello1, Mario U. Mondelli1,2,4

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.