Screening, transmission, prevention, access to care

Strategies to combat liver diseases

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University of Geneva - Switzerland
HBV epidemiology

250-350 million chronically infected – 700,000 deaths per year
Global burden of viral hepatitis from 1990 to 2013 (Global Burden of Disease Study 2013)

Viral hepatitis-related, age-standardized mortality rate, by GBD region
(Overlaid pie charts indicate each virus type's contribution to the total hepatitis-related mortality; the size of the pies are proportional to the hepatitis-attributable mortality for that region)

STANAWAY et al, Lancet 2016
Tools For Control of HBV

• Interruption of transmission
  • Vaccination
  • Birth dose vaccine + HBIG or analogues

• Treatment
  • Nucleoside/Nucleotide analogues
  • Interferons
Before and After Vaccination - Gambia

Vaccine effectiveness: 95%

PETO et al, BMC Infect Dis 2014
Taiwan: Impact of Comprehensive Coverage


NI et al, J Hep 2012
HBV vaccine coverage is still low

Nucleoside Analogues Prevent Disease Progression

Patients With Disease Progression (%)

Time After Randomization (Months)

Placebo (n = 215)
YMDDm (n = 209)
Wild type (n = 221)

Antiviral Therapy Reduces the Risk of HCC

HOSAKA et al, Hepatology 2013
Point-of-care HBsAg assay (Alere) offered to randomly selected communities in Western Gambia and potential blood donors in Banjul

HBsAg screening accepted by 5980 (68.9%) of 8170 community adults and 5559 (81.4%) of 6832 blood donors

HBsAg detected in 495 (8.8%) individuals in communities and 721 (13.0%) blood donors

Linkage to care (visit to liver unit) was high in the communities (402/495, 81.3%) but low (300/721, 41.6%) among people screened at the blood bank

Of those who attended the clinic, 18 (4.4%) patients from the communities and 29 (9.7%) from the blood donors were eligible for treatment (as per EASL guidelines)
Community screening

8,170 eligible for screening in 54 communities (Dec 2011 – Jan 2014)

Absence: 714
Perceived no benefit: 567
Other reasons: 356
Lost to follow-up: 553

5,980 (68.9%, 95% CI: 65.0-72.4%) screened for HBsAg

495 (8.8%, 95% CI: 7.9-9.7%) tested positive for HBsAg

402 (81.3%, 95% CI: 76.6-85.2%) linked to care

18 (4.4%, 95% CI: 2.5-7.7%) eligible for antiviral therapy

Reasons for non-participation:
- Too busy (n=65)
- Feeling ill (n=55)
- Husband refusal (n=43)
- Afraid of bleeding (n=21)
- No trust in MRC (n=11)
- Already tested before (n=4)
- No specific reason given (n=157)

Failure of linkage into care:
- Absence of symptoms
- Poor understanding of disease
- Too busy

LEMOINE et al, Lancet Global Health 2016;4:e559-67
“The high coverage of community-based screening, the good linkage into care, and the small proportion of HBsAg carriers who need treatment suggest that large scale test-and-treat programmes are feasible in sub-Saharan Africa”

LEMOINE et al, Lancet Global Health 2016;4:e559-67
Is screening cost-effective?

USD 540 per DALY averted
USD 511 per QALY gained
USD 645 per life year saved

Must be <3x Purchasing Power Parity-adjusted GDP per capita (WHO)

NAYAGAM et al, Lancet Global Health 2016;4:e568-78
HBsAg prevalence by age and sex in community screening

LEMOINE et al, Lancet Global Health 2016;4:e559-67
Tornado diagram of factors affecting ICER

NAYAGAM et al, Lancet Global Health 2016;4:e568-78
A simulation model of the global HBV epidemic

• Dynamic transmission model, incorporating data on the natural history of HBV, prevalence, mortality, vaccine coverage, treatment dynamics, and demographics
• Age, sex and region structured (21 world regions)
• Generate projections for each scenario (i.e. current interventions and scaling up of existing interventions for prevention of infection and introducing wide-scale population screening and treatment interventions) on:
  • Incidence of chronic new infection
  • Prevalence
  • Deaths due to HBV
  • Costs

NAYAGAM et al, Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]
## Data Inputs and Calibration Strategy

<table>
<thead>
<tr>
<th>Data</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demography</td>
<td>World Population Prospects</td>
</tr>
<tr>
<td>Infant Vaccination coverage</td>
<td>WHO data</td>
</tr>
<tr>
<td>Birth dose vaccination coverage</td>
<td>WHO data</td>
</tr>
<tr>
<td>Treatment availability/coverage</td>
<td>WHO global policy report on prevention &amp; control of viral hepatitis &amp; assumptions</td>
</tr>
<tr>
<td>Natural history parameters</td>
<td>Literature review</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data</th>
<th>Objective</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence patterns of HBsAg+</td>
<td>Informs burden and historic pattern of infection</td>
<td>OTT et al, Vaccine 2012</td>
</tr>
<tr>
<td>Prevalence patterns of HBeAg+</td>
<td>Informs patterns of new cases of chronic infection and transmission</td>
<td>OTT et al, BMC Inf Dis 2012</td>
</tr>
<tr>
<td>Cancer death estimates</td>
<td>Informs burden of disease and stages of disease progression for chronically infected</td>
<td>GLOBOCAN 2012</td>
</tr>
</tbody>
</table>

NAYAGAM et al, Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]
## Public Health Intervention Scenarios

<table>
<thead>
<tr>
<th>Intervention Scenarios</th>
<th>Infant Vaccination Coverage</th>
<th>Birth Dose Vaccination Coverage</th>
<th>Coverage of Peri-Partum Treatment (PPT) for HBeAg+ mothers</th>
<th>Access to treatment ²</th>
<th>Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Historic Intervention</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>No</td>
</tr>
<tr>
<td>Status Quo</td>
<td>Continues at current levels</td>
<td>Continues at current levels</td>
<td>No coverage currently</td>
<td>Continues at current levels (categorised by region)</td>
<td>No</td>
</tr>
<tr>
<td>Infant Vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Vaccination + BD Vaccination</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Vaccination + BD Vaccination + PPT</td>
<td>90%</td>
<td>80%</td>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Vaccination + BD Vaccination + PPT + Treatment</td>
<td></td>
<td></td>
<td>80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infant Vaccination + BD Vaccination + PPT + Treatment + Cure</td>
<td></td>
<td></td>
<td>80%</td>
<td></td>
<td>2025</td>
</tr>
</tbody>
</table>

NAYAGAM et al, Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]
Tenofovir for prophylaxis of mother-to-child transmission (PMTCT)
Control of incidence of new chronic HBV carriage

NAYAGAM et al, Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]
Control of Mortality

NAYAGAM et al, Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]
How Much Would it Cost?

NAYAGAM et al, Lancet Infect Dis 2016 Sep 13 [Epub ahead of print]
Epidemiology of Hepatitis C

130–170 million persons are infected with hepatitis C virus (HCV)

- ~350,000 people die annually of HCV-related diseases

- Highest prevalence in Central and East Asia and North Africa

- Bloodborne virus
  - Injecting drug use
  - Inadequate sterilization of medical equipment
  - Transfusion of unscreened blood

- Currently no vaccine

- Very powerful, safe antivirals

HCV is a hidden epidemic, especially in developing countries

- Most hepatitis cases in low & middle income countries
- Insufficient/No surveillance systems
- No systematic screening of key populations
- Stigmatization
- Penalization
- Expensive diagnostic tools

LEMOINE et al, J Hepatol 2015
PWIDs are a key population

HCV seroprevalence among PWIDs worldwide (~50% of 16,000,000)

Also people in Africa inject drugs!

<table>
<thead>
<tr>
<th></th>
<th>Senegal</th>
<th>Tanzania</th>
<th>Kenya</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated number of IDUs</td>
<td>1,323 (Dakar)</td>
<td>15,000 (Dar el Salaam)</td>
<td>20 - 30,000</td>
</tr>
<tr>
<td>HCV prevalence</td>
<td>39%</td>
<td>28%</td>
<td>39-59%</td>
</tr>
</tbody>
</table>

LEPRETRE & LEMOINE (personal communication)
15% of worldwide prisoners are anti-HCV+

DOLAN et al, Lancet 2016
Evolution of HCV Treatment

- Genotype 1
- Genotype 2&3
- Genotype 4

- IFN Mono
- PEG Mono
- IFN + RIBA
- PEG + RIBA
- PI + PEG + RIBA
- DAA x 2
The treatment *cascade* in the US: a meta-analysis

- Chronic HCV-Infected: 100%
- Diagnosed and Aware: 50%
- Access to Outpatient Care: 43%
- HCV RNA Confirmed: 27%
- Underwent Liver Biopsy: 17%
- Prescribed HCV Treatment: 16%
- Achieved SVR: 9%
The Swiss model: assuming a SVR rate of 95% in 2016 and a constant number of treated patients (1,100 per year), the incidence of HCC and liver-related deaths in 2030 will decrease by ~10% only.
Estimated increase of treatment rate to reduce prevalence by 90% in 2030

- Denmark
- Ireland
- Brazil
- Portugal
- Slovak Republic
- Belgium
- Egypt
- New Zealand
- Czech Republic
- Sweden
- England
- Austria
- Germany
- Poland
- Norway
- Luxembourg
- Spain
- France
- Portugal

Annual Treatment Rate (%) at Baseline

Fold Increase in Tx Rate to Achieve 90% Reduction
PPP-adjusted financial impact of treatment coverage for all patients with HCV

<table>
<thead>
<tr>
<th>Country</th>
<th>Adult Population Infected with Viraemic HCV</th>
<th>Cost of Treatment Coverage (in Millions of PPP Dollars)</th>
<th>Ledipasvir/Sofosbuvir</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Point Estimate</td>
<td>Lower Estimate</td>
<td>Upper Estimate</td>
</tr>
<tr>
<td>United States</td>
<td>2,575,000</td>
<td>2,377,000</td>
<td>4,754,000</td>
</tr>
<tr>
<td>Japan</td>
<td>1,252,000</td>
<td>423,000</td>
<td>1,899,000</td>
</tr>
<tr>
<td>Italy</td>
<td>768,000</td>
<td>615,000</td>
<td>2,805,000</td>
</tr>
<tr>
<td>Turkey</td>
<td>434,000</td>
<td>274,000</td>
<td>959,000</td>
</tr>
<tr>
<td>Spain</td>
<td>472,000</td>
<td>109,000</td>
<td>719,000</td>
</tr>
<tr>
<td>Poland</td>
<td>196,000</td>
<td>134,000</td>
<td>259,000</td>
</tr>
<tr>
<td>Brazil</td>
<td>1,939,000</td>
<td>1,371,000</td>
<td>2,008,000</td>
</tr>
<tr>
<td>Egypt</td>
<td>5,623,000</td>
<td>3,940,000</td>
<td>6,885,000</td>
</tr>
</tbody>
</table>

123.5% of total PPP-adjusted pharmaceutical expenditure

What does elimination mean?

**Elimination:** the reduction of an infectious disease's incidence in a regional population to zero, or the reduction of the global prevalence to a negligible amount

**Eradication:** the reduction of an infectious disease's incidence in the global population to zero
Requirements for elimination

1. No animal reservoir

2. The disease should be clearly identifiable/accurate diagnostic tools should exist

3. Country, region and global surveillance systems

4. An efficient and practical intervention must be available to interrupt transmission

5. Economic considerations as well as societal and political support and commitment
The WHO impact targets for elimination

90% reduction in new cases of chronic HBV and HCV infection

65% reduction in deaths from chronic HBV and HCV

Courtesy of Stefan Wiktor, WHO 2016
Hepatitis awareness is poor

Mombassa (Kenya):
Out of 400 IDUs (59% anti-HCV+) 369 (92%) did not know their HCV status as they had never been tested (LEMOINE, personal communication)

Gambia (West Africa):
Out of 489 participants screened in 2013 for HBV, only two persons (0.4%) had heard about HBV infection and had been tested for HBV in the past

None of the positive individuals were previously tested and knew their status

LEMOINE et al, Lancet Global Health 2016
Summary

• HBV & HCV are under-appreciated causes of mortality in LMIC
• Awareness about hepatitis in some geographical areas is very low
• Vaccination is effective at prevention of new chronic cases of HBV
• PMTCT required for elimination of HBV
• Mortality cannot be controlled in the foreseeable future without screening and increased treatment uptake
• Current costs of HCV drugs makes elimination programs unaffordable even for rich countries