Prediction of HCV-related morbidity and mortality burden in France

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Introduction

• HCV burden depends on
  – Number of subjects infected with HCV
  – Stage of disease for these subjects
  – Natural history of HCV and treatment
• Difficult to measure directly
• Epidemiological data are limited
  ➔ Mathematical modeling is an useful approach
Backcalculation method

Age at disease diagnosis

= 

Age at infection + Time to disease development

• Combination of
  – Existing statistics about the number of reported cases
  – Mathematical representation of the time course between infection and disease diagnosis
HCV backcalculation

- Reported HCC mortality
- HCV model with published epidemiological data

To backcalculate past incidence of HCV

To project HCV-related mortality
Process

- **Initialization**: Set the unknown parameters to initial values
- **Estimation**: Age- and sex- stratified cohorts simulated by year through the model of HCV progression until death
- **Minimization**
  - To fit the 500,000 HCV chronic carriers in 1994, a standardization factor applied to all estimated numbers
  - Observed and predicted HCV-related deaths from HCC compared using the weighted least squares criterion
- **Iteration**: The process repeated until a minimum value of the weighted least squares criterion was obtained
Predictions

• Estimated parameters are used to predict
  – HCV-related deaths from HCC due to pre-1996 infections and in the absence of effective therapy (preliminary model)
  – HCV-related deaths from HCC and liver failure due to pre-1999 infections, taking into account treatment effects (updated model)
Plan

1) Preliminary HCV model (Deuffic et al, Hepatology 1999)
   - 1979-1995 data
   - No treatment

2) Updated HCV model (Deuffic-Burban et al, J Hepatol 2004)
   - 1979-1998 data
   - Including treatment effects
Preliminary HCV model

Recovery from infection
30%

Infection? → Chronic Hepatitis 70%

Chronic Hepatitis

pD

Death from competitive causes
30%

Preliminary HCV model

Death from liver failure without HCC 4%

Cirrhosis

pD

Death from competitive causes
70%

pC(sex,age)?

HCC

4%

HCC death related to HCV 33%

Recovery from infection
Assumptions

• Past incidence curve modeled by a logistic function
  – modified in 1990 by a 60%-factor to account for the screening of blood donations

• Age and sex distribution at infection obtained from three French cohorts
  (Poynard et al, Lancet 1997)
HCC mortality data

• By age and gender, between 1979 and 1995 (French national database CepiDC)
• Assuming that 36% were attributed to HCV = weighted mean of the estimate of three studies
  – Zarski et al, J Hepatol 1991 (20%)
  – Ducreux et al, Lancet 1990 (28%)
  – Nalpas et al, J Hepatol 1991 (58%)
Results

Blood screening for HCV in 1990

HCV incidence by year

HCC deaths attributable to HCV per year

Men (observations)  Women (observations)
Men (model estimations)  Women (model estimations)
Men (model predictions)  Women (model predictions)
Updated HCV model

Recovery from infection

Infection?

25%  75%

Treatment-induced recovery

Chronic Hepatitis

0.5% to 6%

p_C(sex,age)?

Death from competitive causes

p_D

Cirrhosis

Death from liver failure without HCC

0.028 \times 1.04^{(age-57)}

HCC

Death from HCC related to HCV

0.028 \times 1.05^{(age-57)}

35% to 57%

Recovery from infection

Treatment-induced recovery

Chronic Hepatitis

Cirrhosis

HCC
Treatment

- Antiviral treatment effects (one-line therapy)
  - Likelihood of treatment was 5% in 1991-1994, 10% in 1995-1998, 15% in 1999
  - Likelihood of becoming viral negative was 10% in 1991-1994, 20% in 1995-1998, 40% in 1999
- Hypothetical scenario of mass screening and treatment with PEG-IFN+RIBAVIRIN in 2001
  - 50% of treatment coverage and PVR=60%
  - 100% of treatment coverage and PVR=60%
Assumptions

• Past incidence curve modeled by a logistic function until 1990
  – Reduced in 1990 by a 60%-factor and constant from 1990 to 1994
  – Reduced again in 1995 by a 50%-factor and constant from 1995 to 1998

• Age and sex distribution at infection
  (Poynard et al, Lancet 1997)
HCC mortality data

- By age and gender, between 1979 to 1998 (CepiDC)
- Assuming that 27% were attributed to HCV (Bréchot 1998)
- Sensitivity analysis
  - Constants: 15% and 40%
  - Increasing functions taking the values of 5% in 1979 and 27% in 1998: linear and exponential
Results

**HCV incidence per year**

- Blood screening for HCV in 1990
- Public knowledge of the risks of HCV

**Mortality related to HCV**

- Total predicted deaths 2001-2021 by fitted model
  - 85,000 [80,000-89,000] with present treatment
  - 70,000 [66,000-73,000] with a 50%-coverage
  - 55,000 [52,000-58,000] with a 100%-coverage

**Predictions by fitted model with present treatment**
- Predictions by fitted model with a treatment coverage of 50%
- Predictions by fitted model with a treatment coverage of 100%
Sensitivity analysis

HCV incidence per year

Blood donors screening in 1990

Public knowledge of the risks of HCV from 1995

Mortality related to HCV

Total predicted deaths 2001-2021 by fitted model
Constant = 27%: 85,000 [80,000-89,000]
Constant = 15%: 58,000 [53,000-62,000]
Constant = 40%: 105,000 [97,000-112,000]
Linear assumption (5%-27%): 102,000 [98,000-105,000]
Exponential assumption (5%-27%): 98,000 [95,000-102,000]
Morbidity and mortality in 2002 and 2022

- Estimates with updated model
- Two scenarios tested
  - S1: no treatment of cirrhosis
  - S2: hypothetical treatment of 100% of subjects with cirrhosis in 2002 that would cure 50% of them
## Results (Expertise Collective INSERM 2003)

<table>
<thead>
<tr>
<th></th>
<th>2002</th>
<th>2022</th>
<th>S1</th>
<th>S2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>478,000</td>
<td>282,000</td>
<td>261,000</td>
<td></td>
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<tr>
<td>Chronic hepatitis</td>
<td>431,000</td>
<td>234,000</td>
<td>234,000</td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>45,000</td>
<td>45,000</td>
<td>26,000</td>
<td></td>
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<tr>
<td>HCC</td>
<td>2,000</td>
<td>2,800</td>
<td>1,600</td>
<td></td>
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<tr>
<td>HCV-related deaths</td>
<td>3,300</td>
<td>4,500</td>
<td>2,500</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

- Mathematical models provide back and future projections of HCV burden
- Projections need to be updated when new data become available
- Limitations:
  - Inadequacy or lack of data
  - Delay due to « time-modeling »