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

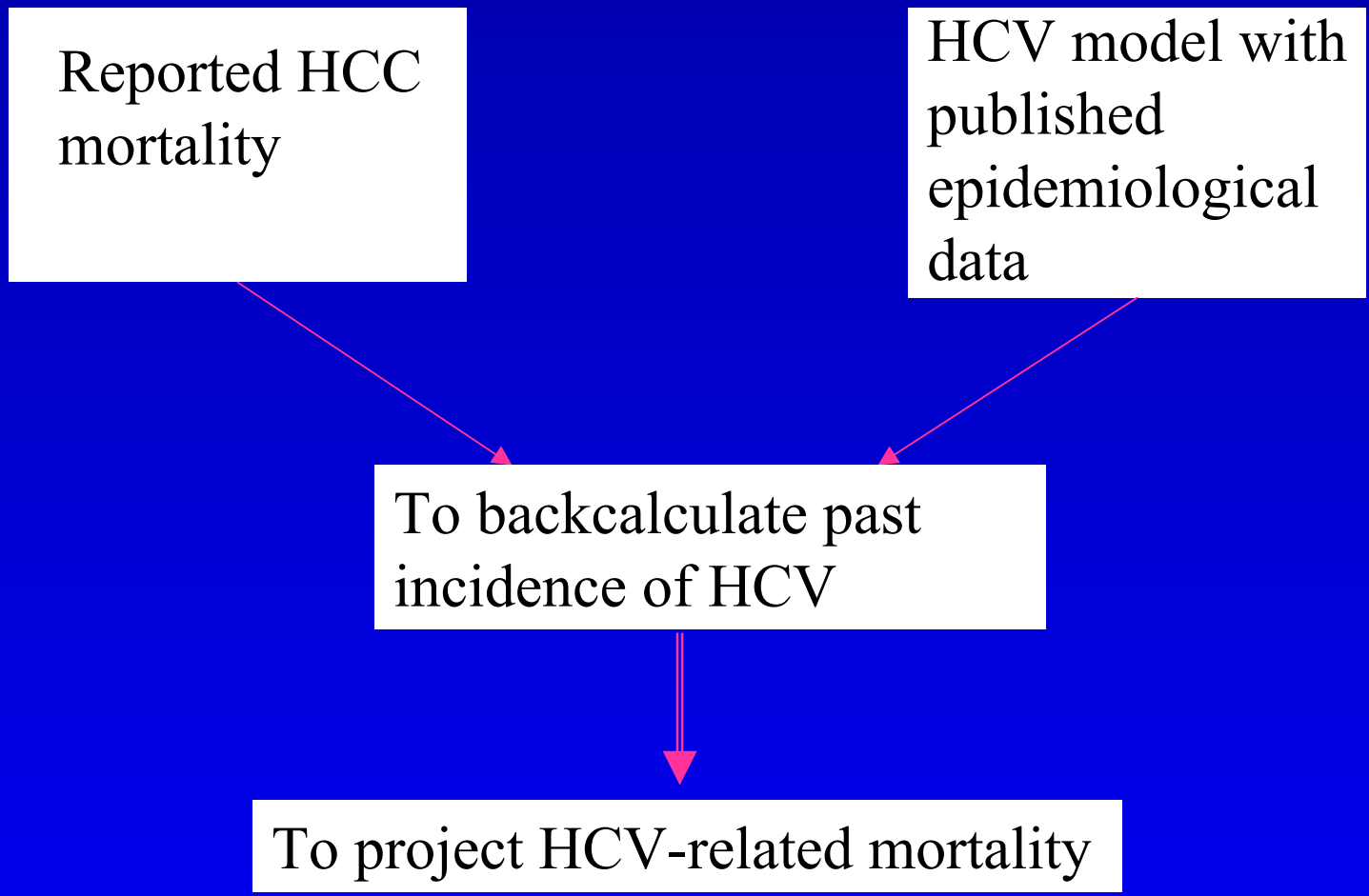
Age at disease diagnosis

=

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



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

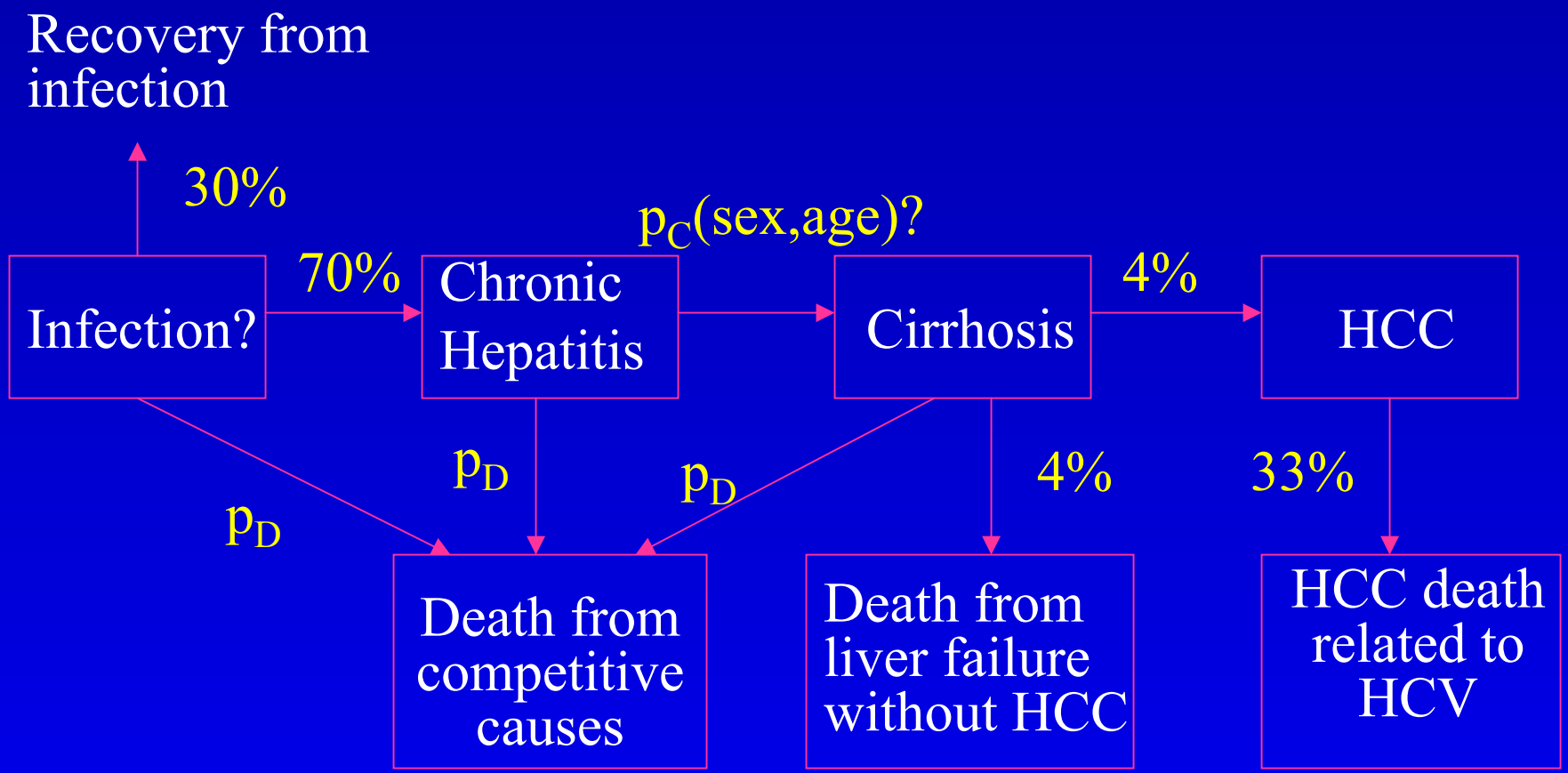
Predictions

- 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



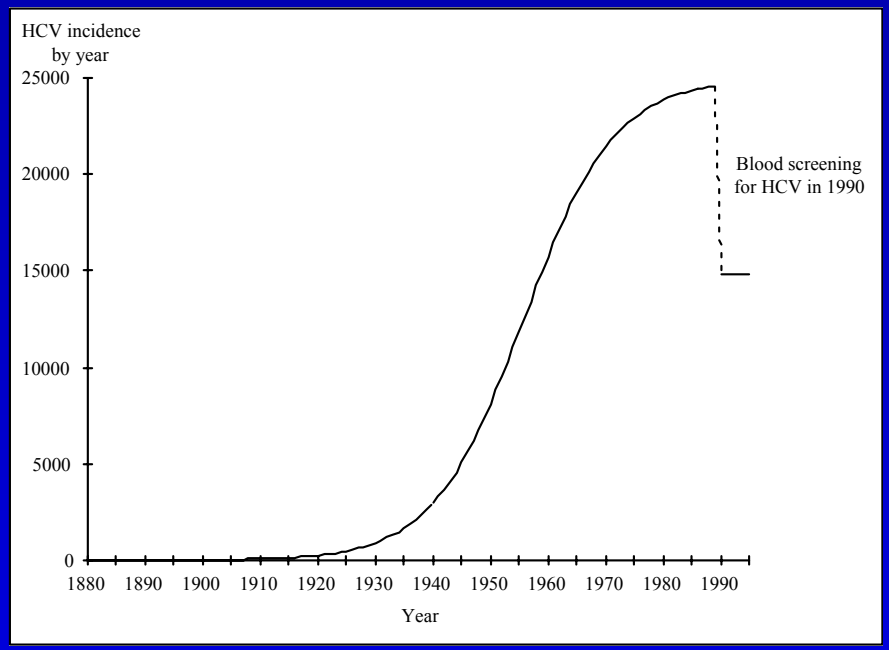
Assumptions

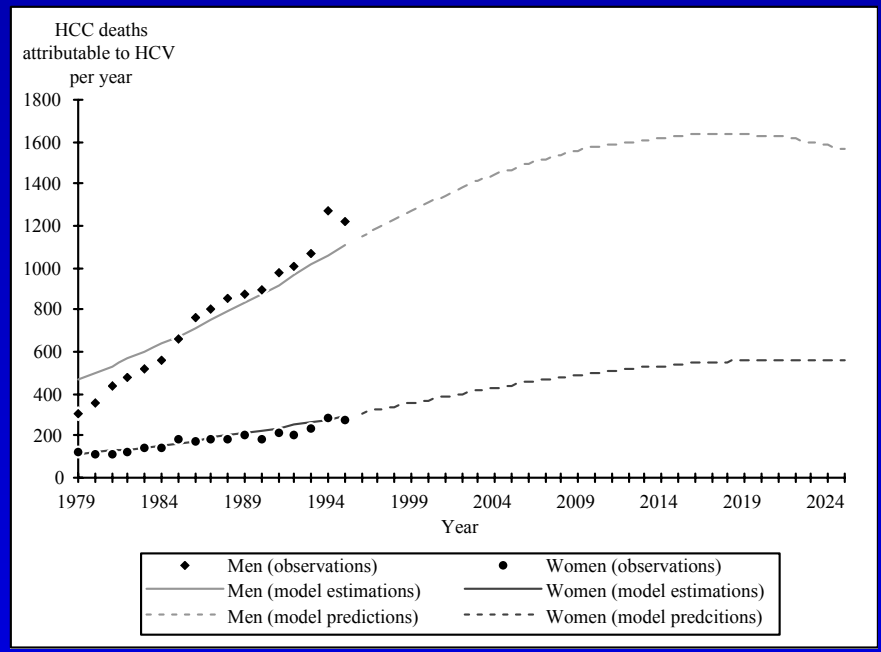
- Past incidence curve modeled by a logistic function
  - modified in 1990 by a 60%-factor to account for the screening of blood donations
- Age and sex distribution at infection obtained from three French cohorts (Poynard et al, Lancet 1997)

HCC mortality data

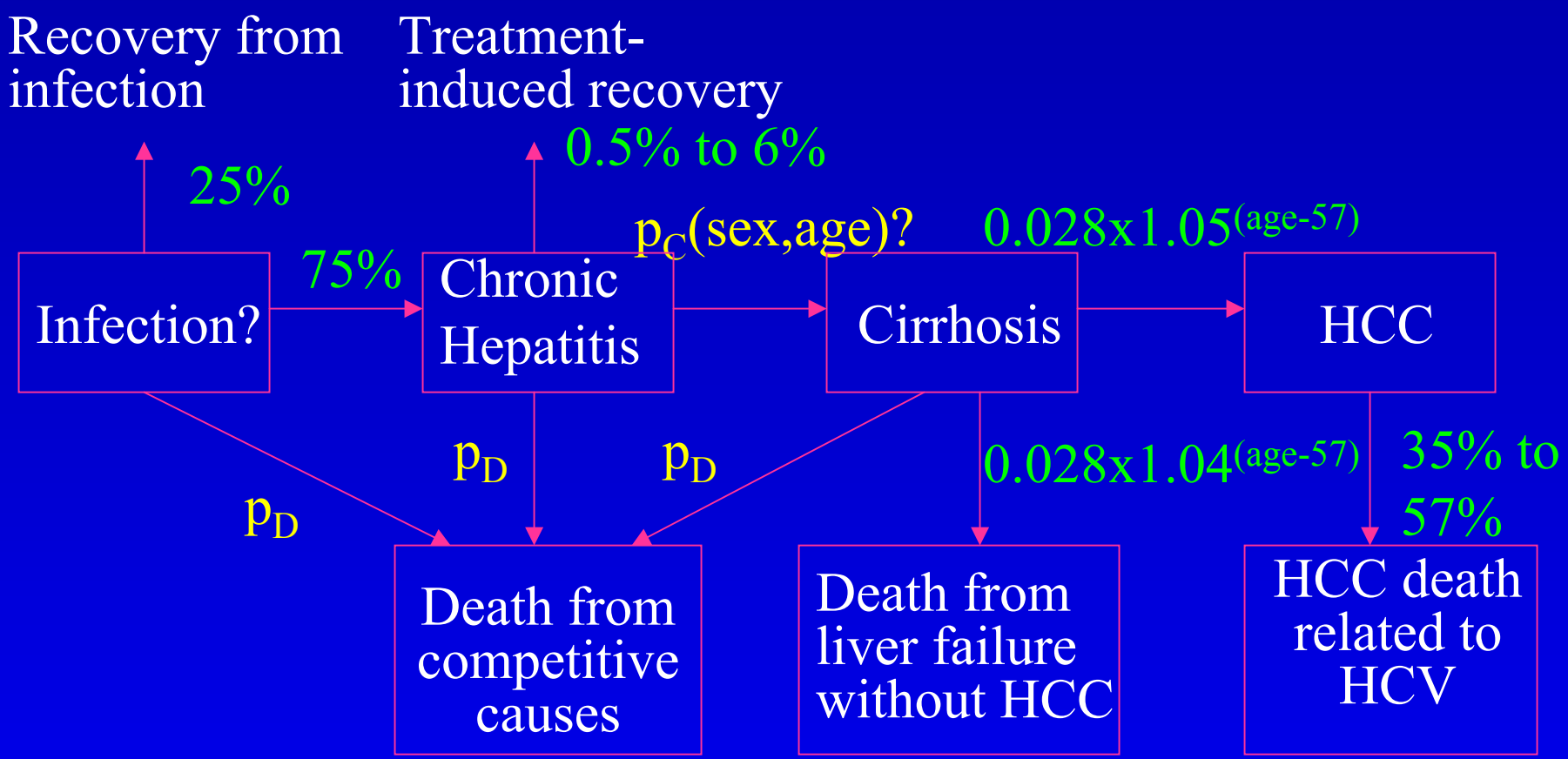
- By age and gender, between 1979 and 1995 (French national database CepiDC)
- Assuming that 36% were attributed to HCV = weighted mean of the estimate of three studies
  - Zarski et al, J Hepatol 1991 (20%)
  - Ducreux et al, Lancet 1990 (28%)
  - Nalpas et al, J Hepatol 1991 (58%)

Results


HCV incidence
by year
25000
20000
15000
10000
5000
0
1880 1890 1900 1910 1920 1930 1940 1950 1960 1970 1980 1990
Year
Blood screening
for HCV in 1990


HCC deaths
attributable to HCV
per year
1800
1600
1400
1200
1000
800
600
400
200
0
1979 1984 1989 1994 1999 2004 2009 2014 2019 2024
Year
Men (observations)
Women (observations)
Men (model estimations)
Women (model estimations)
Men (model predictions)
Women (model predcitions)

Updated HCV model



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%

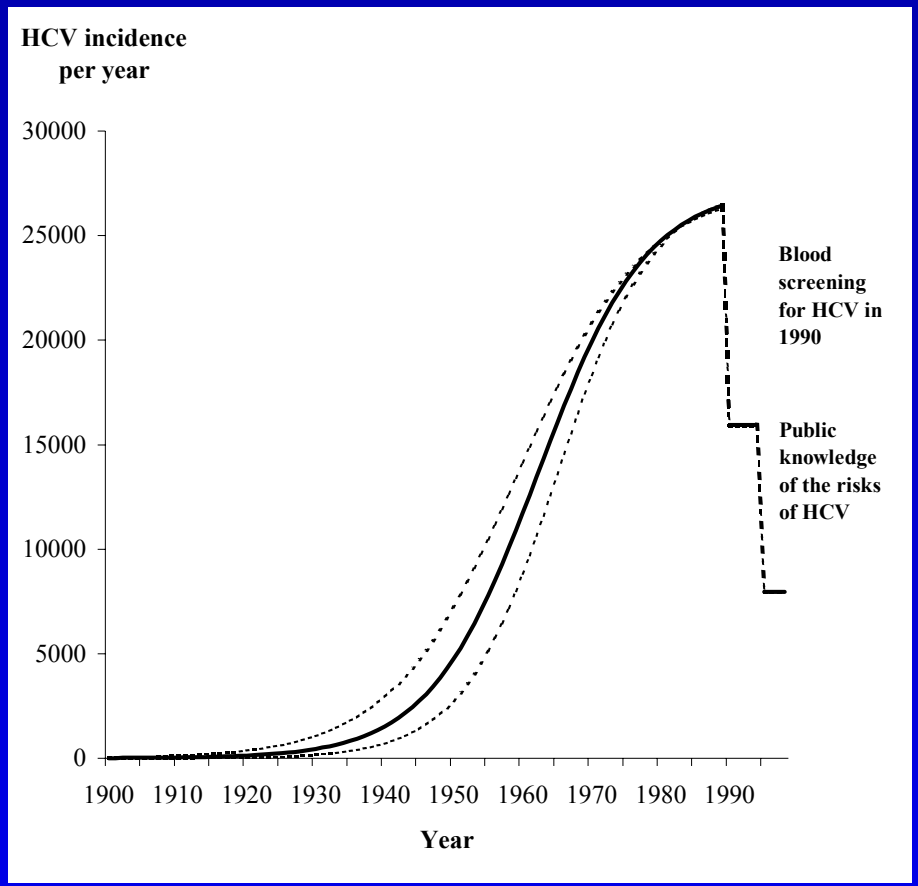
Assumptions

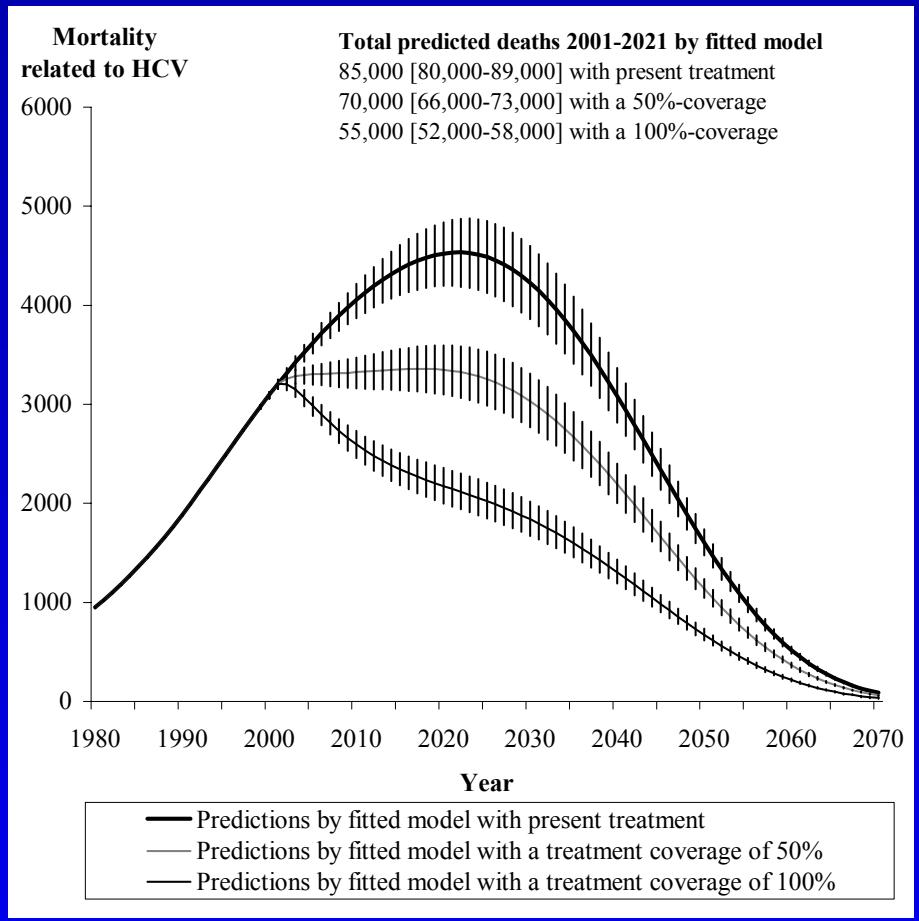
- Past incidence curve modeled by a logistic function until 1990
  - Reduced in 1990 by a 60%-factor and constant from 1990 to 1994
  - Reduced again in 1995 by a 50%-factor and constant from 1995 to 1998
- Age and sex distribution at infection (Poynard et al, Lancet 1997)

HCC mortality data

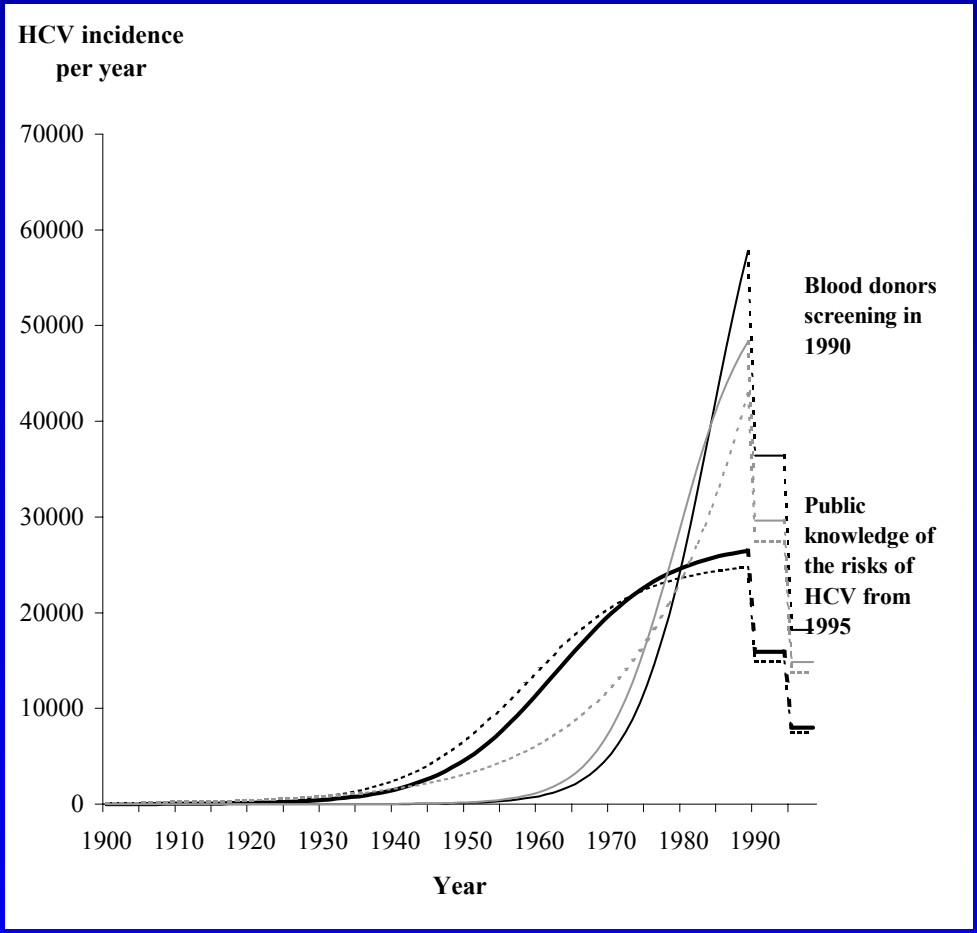
- By age and gender, between 1979 to 1998 (CepiDC)
- Assuming that 27% were attributed to HCV (Bréchot 1998)
- Sensitivity analysis
  - Constants: 15% and 40%
  - Increasing functions taking the values of 5% in 1979 and 27% in 1998: linear and exponential

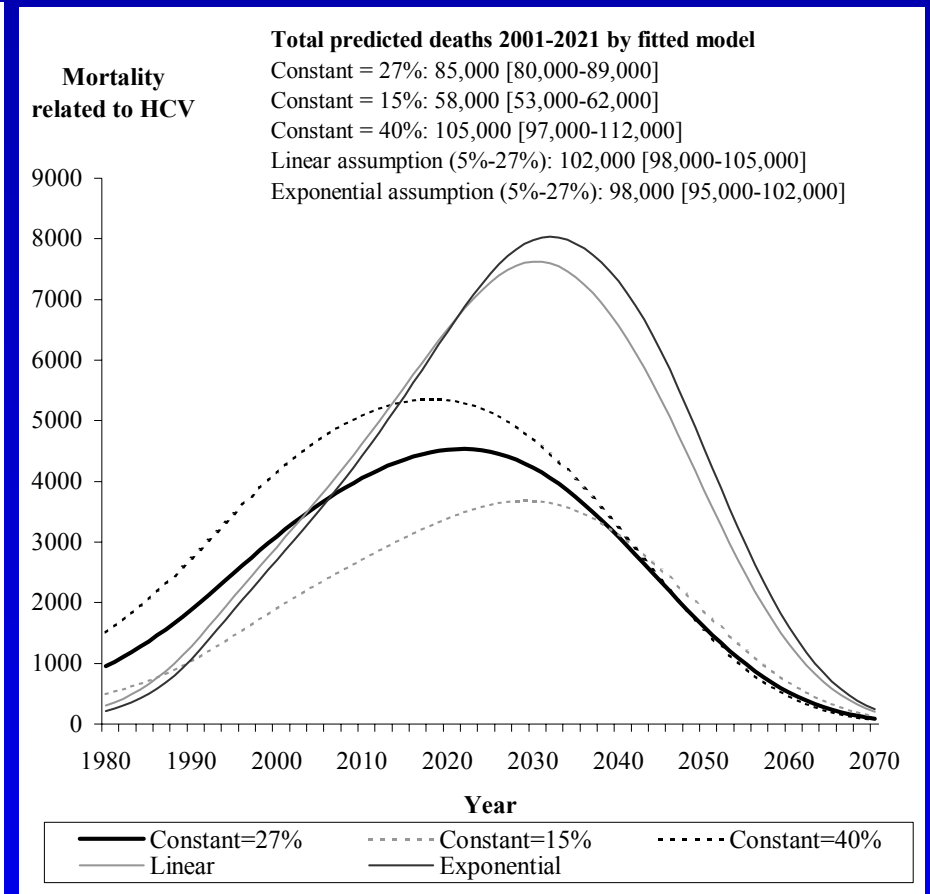
Results


HCV incidence per year
30000
25000
20000
15000
10000
5000
0
1900 1910 1920 1930 1940 1950 1960 1970 1980 1990
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
6000
5000
4000
3000
2000
1000
0
1980 1990 2000 2010 2020 2030 2040 2050 2060 2070
Year
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





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)

	2002	2022	
		S1	S2
Prevalence	478,000	282,000	261,000
Chronic hepatitis	431,000	234,000	234,000
Cirrhosis	45,000	45,000	26,000
HCC	2,000	2,800	1,600
HCV-related deaths	3,300	4,500	2,500

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 »