

# Le futur de l'Hépatologie

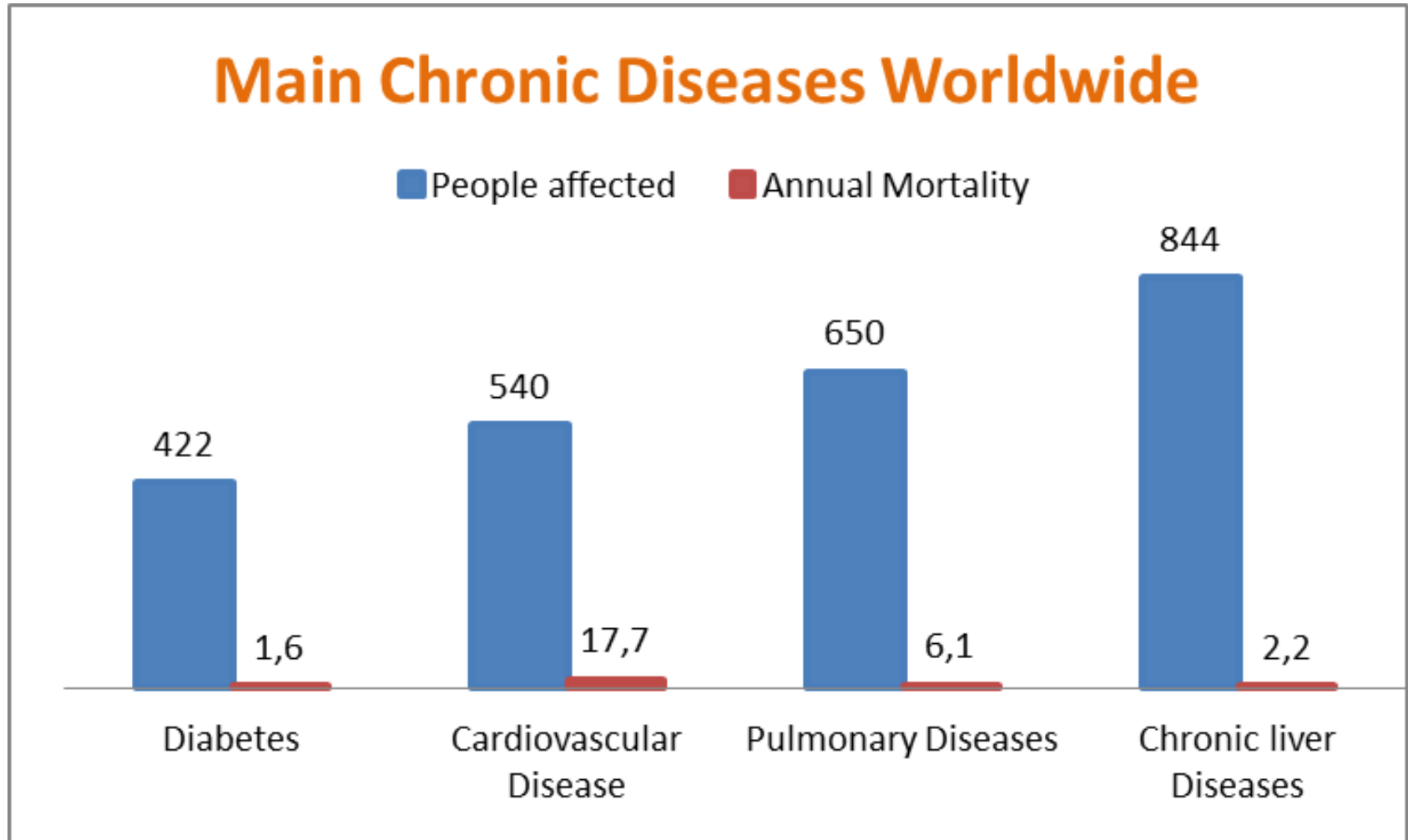
Patrick Marcellin

Service d'hépatologie et INSERM CRI, Hôpital Beaujon  
Direction de la Recherche Clinique et de l'Innovation, APHP

CLDs

A Very High Prevalence

# Global main chronic diseases and CLDs



The keys figures are in million of people or deaths

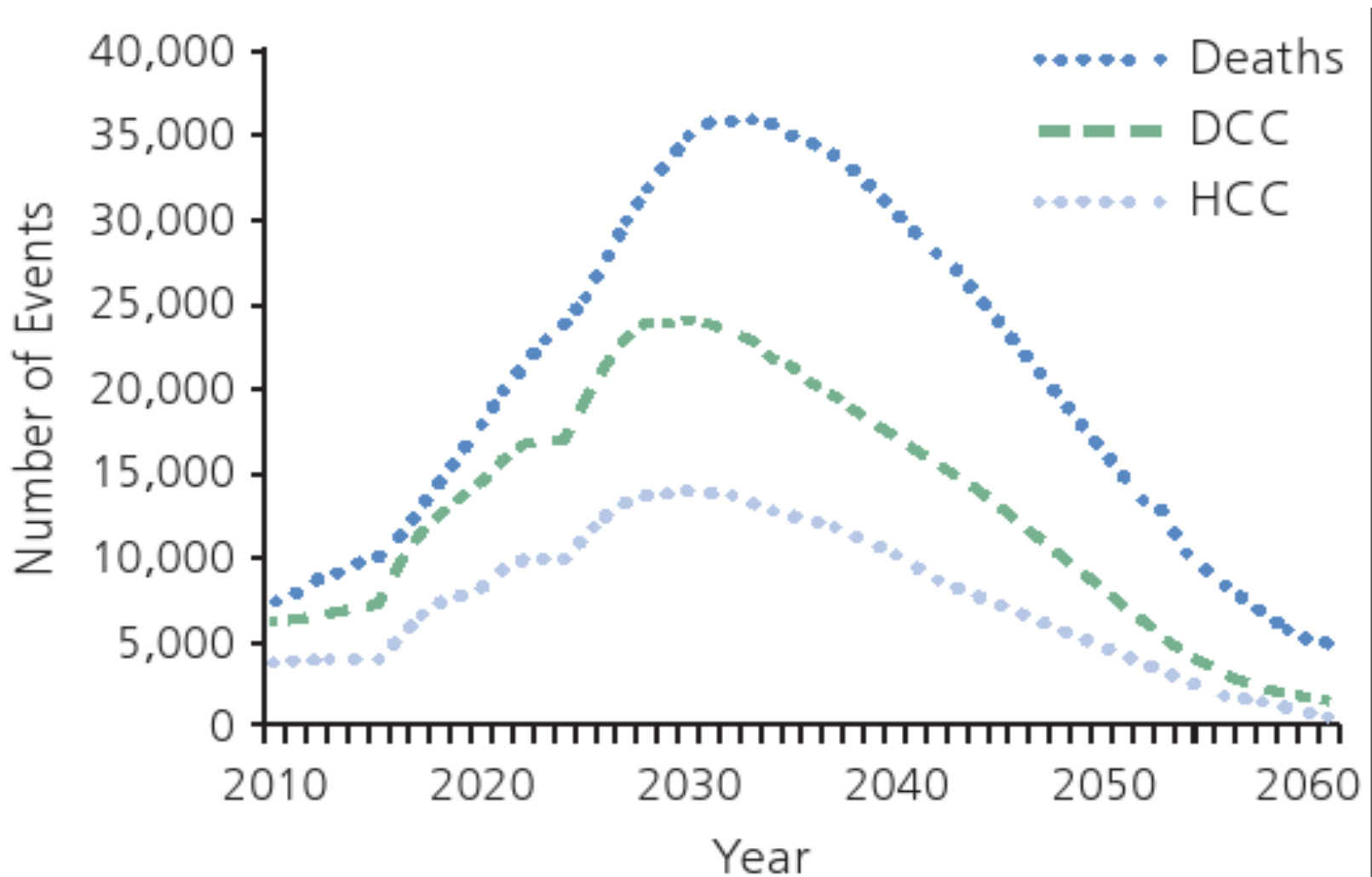
# Global Burden of CLDs

- Prevalence of CLDs : **18,5%**
- Prevalence of cirrhosis: **4.5% to 9.5%**
- Annual incidence of cirrhosis: **633,000**
- Liver transplantations per year: **26,000**
- Annual incidence of HCC: **5.6%**
- HCC one of the most common cancers: **4th**

CLDs

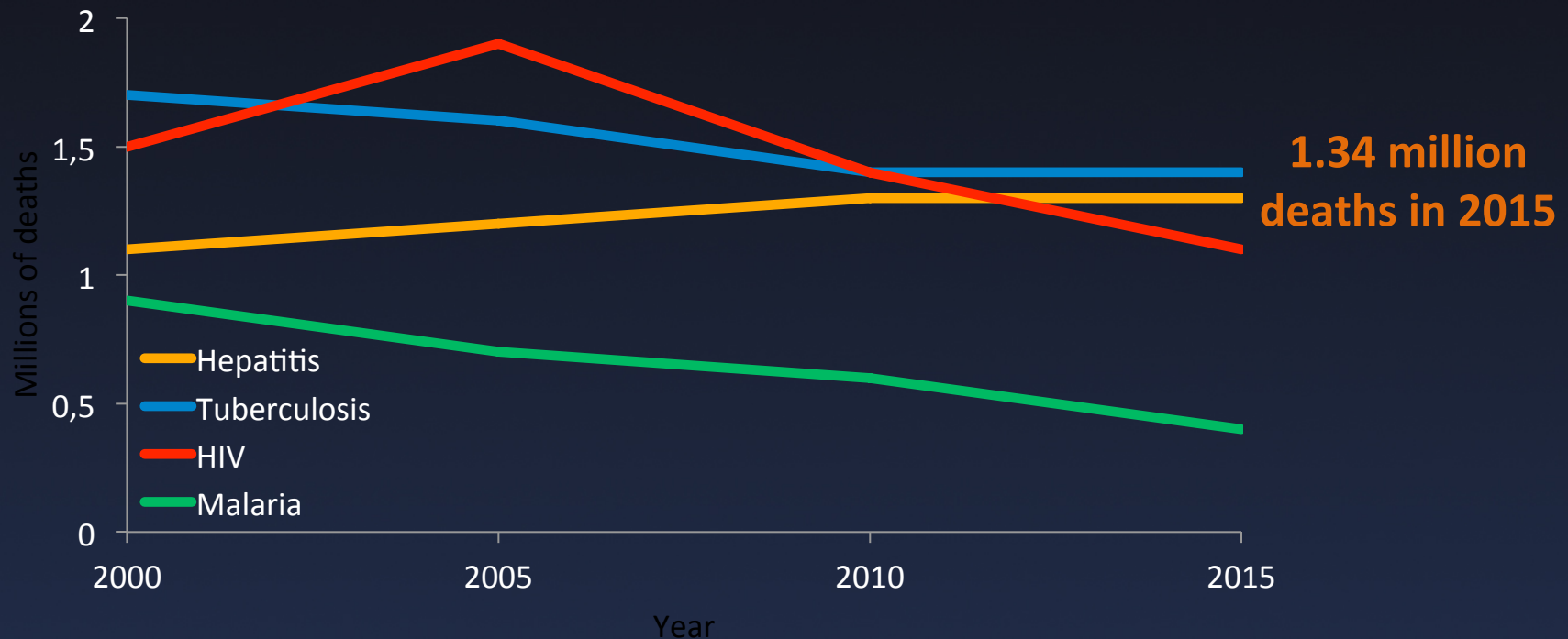
A High Morbidity and Mortality

# Forecasting the morbidity and mortality associated with HCV in US



# Viral hepatitis related mortality

## *WHO Global Hepatitis Report 2017*



**96% of deaths are related to HBV and HCV (cirrhosis and HCC )**

CLDs

A High and Increasing  
Public Health Burden



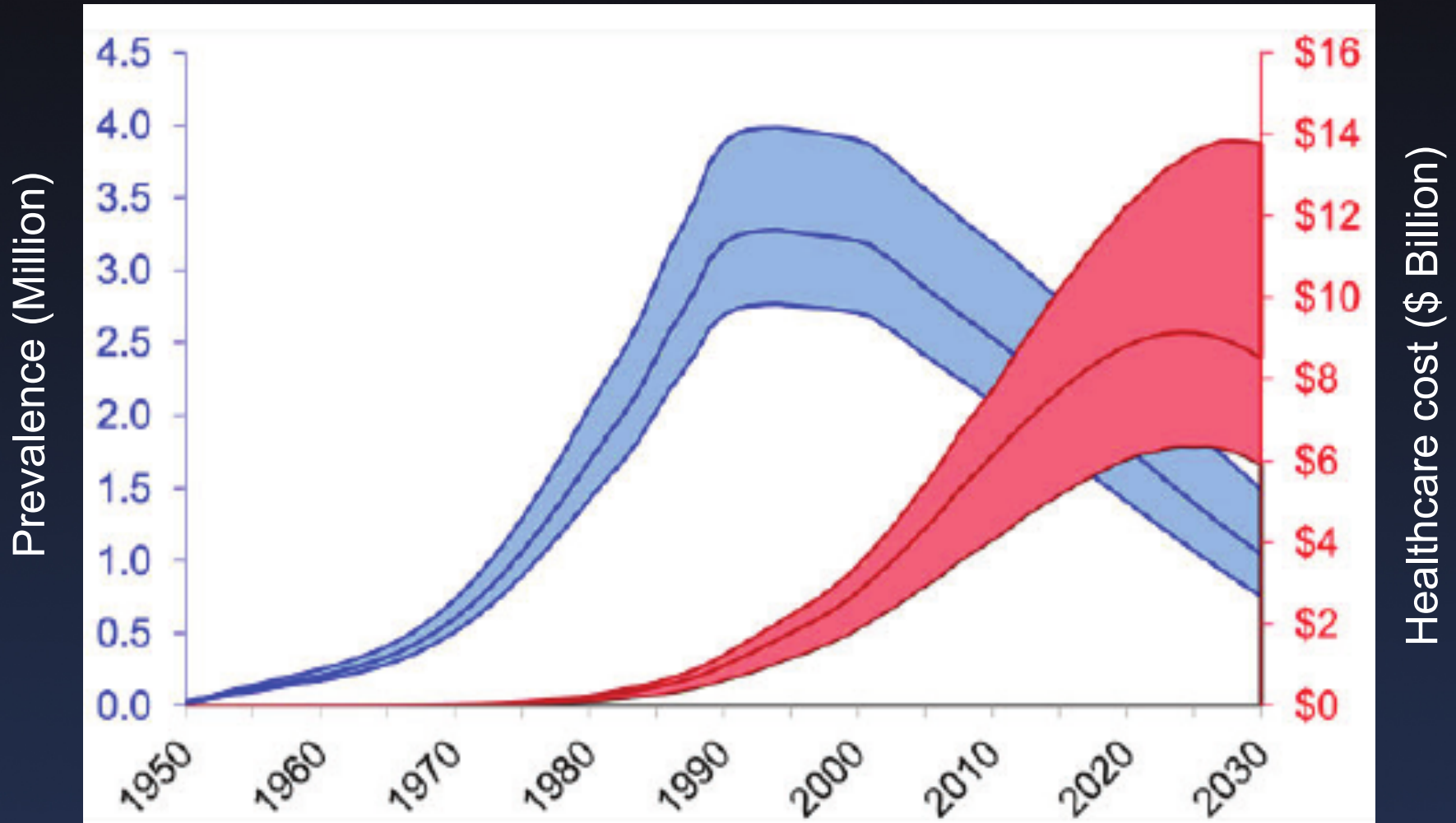
# The economic burden of CLDs

There are no data for the global cost.

Data from US:

- HBV: \$9 billion
- HCV: \$10,6 billion (before DAAs)
- ALD: \$24,5 billion
- NAFLD: \$103 billion
  
- Annual cost/patient with end-stage HCV CLD: \$60,000
- 3-year cost/patient with LT: \$540,000

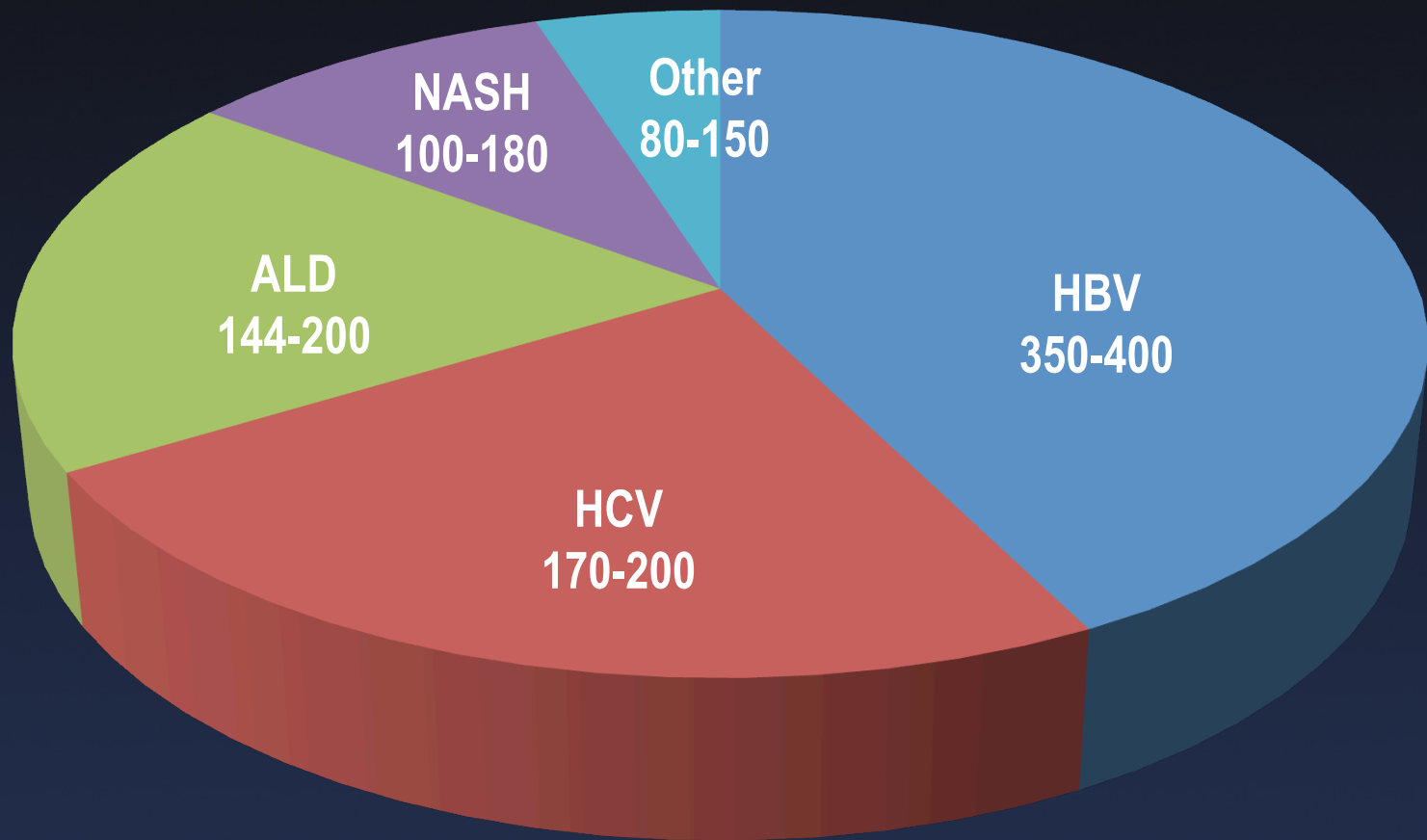
# Total prevalence of CHC and healthcare cost in the US 95% Cis



CLDs

A Changing Pattern

# Number of patients with CLD (millions)

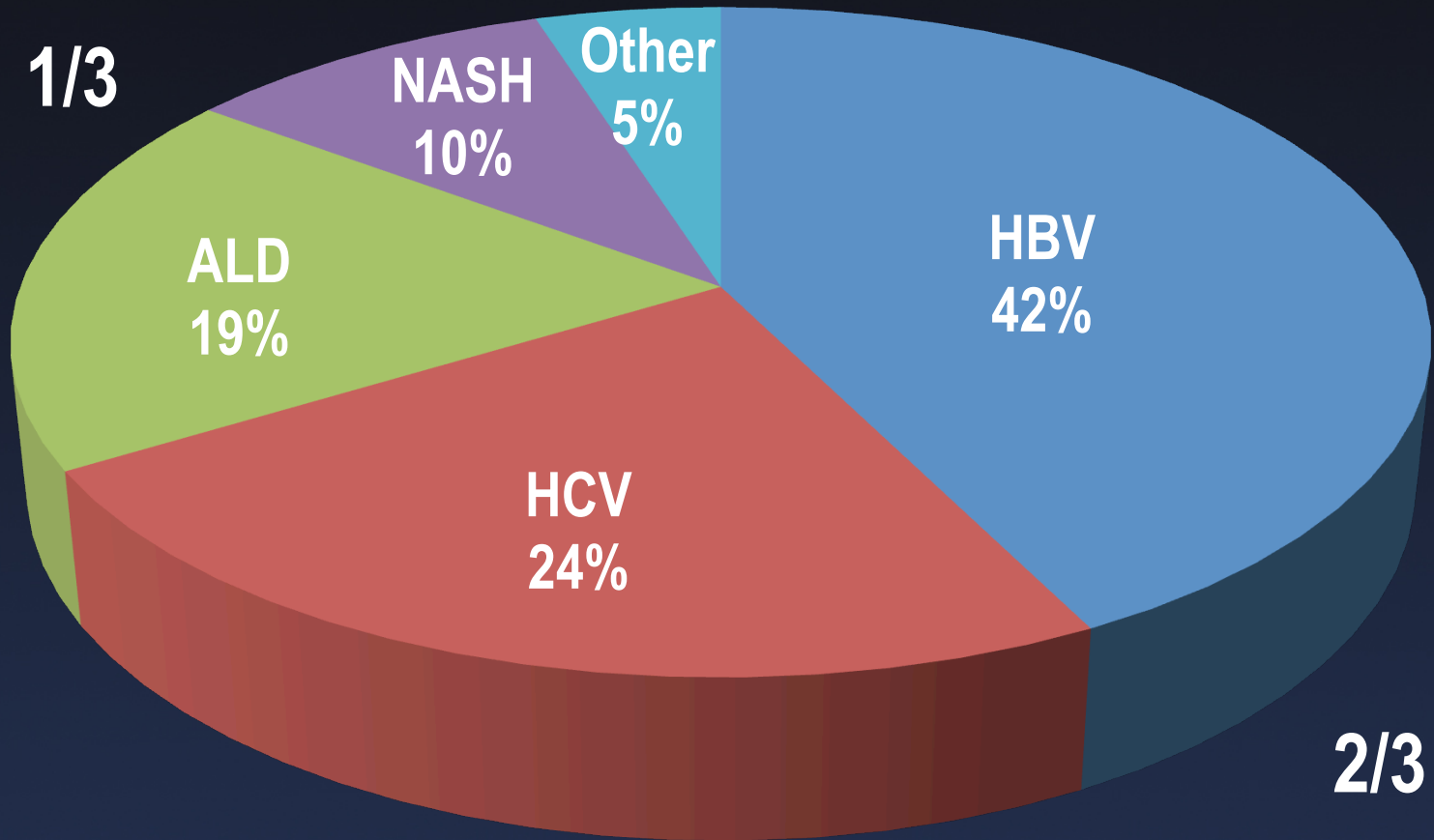


Estimation worldwide: 844 to 1,130 millions

# Chronic liver diseases: today

## Non Viral CLDs

1/3



ALD  
19%

NASH  
10%

Other  
5%

HBV  
42%

HCV  
24%

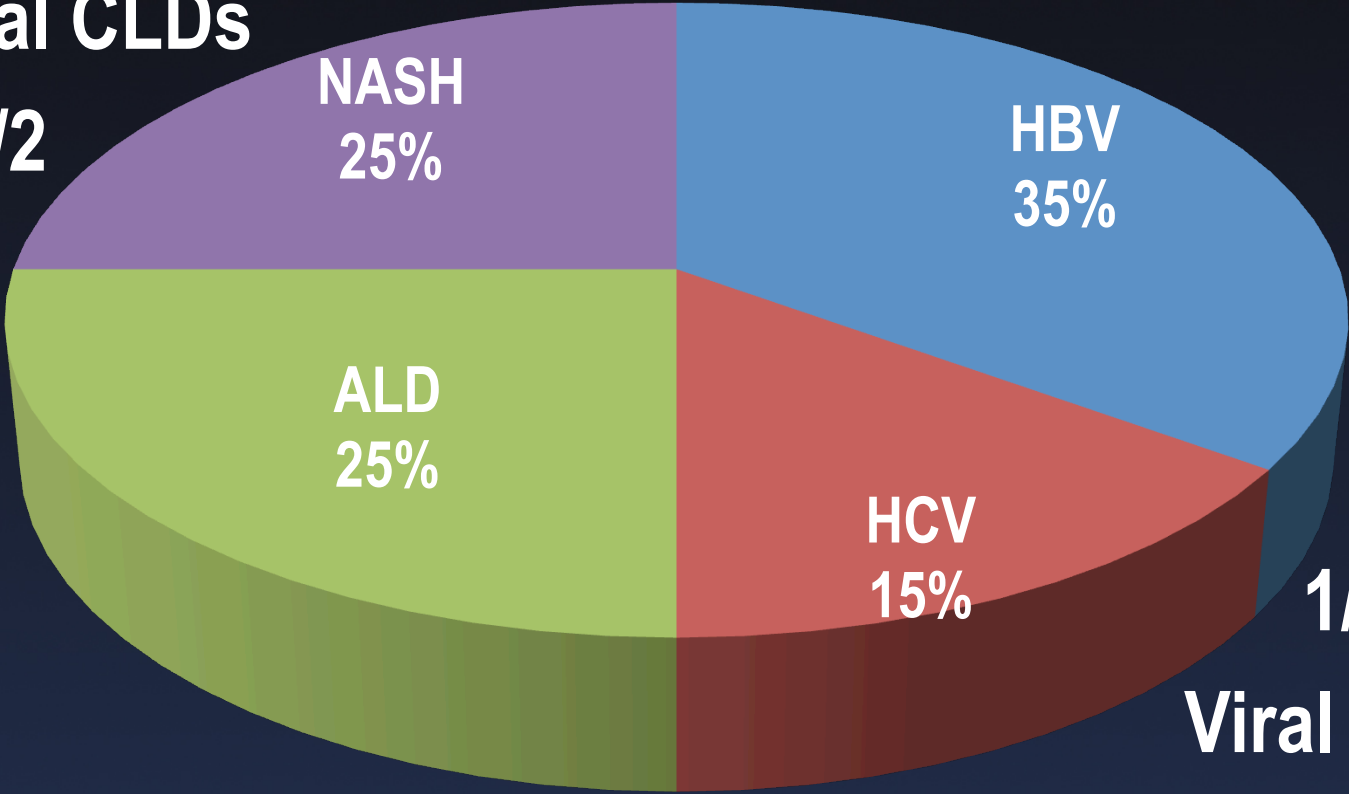
2/3

Viral CLDs

# Chronic liver diseases: the future (10 years)

**Non Viral CLDs**

**1/2**



**1/2**  
**Viral CLDs**

**Decrease of viral CLDs**  
**Increase of non viral CLDs**

# Elimination of HCV

## A mythe or a reality?



# **WHO 2017: Elimination of Hepatitis C a global Public Health priority**

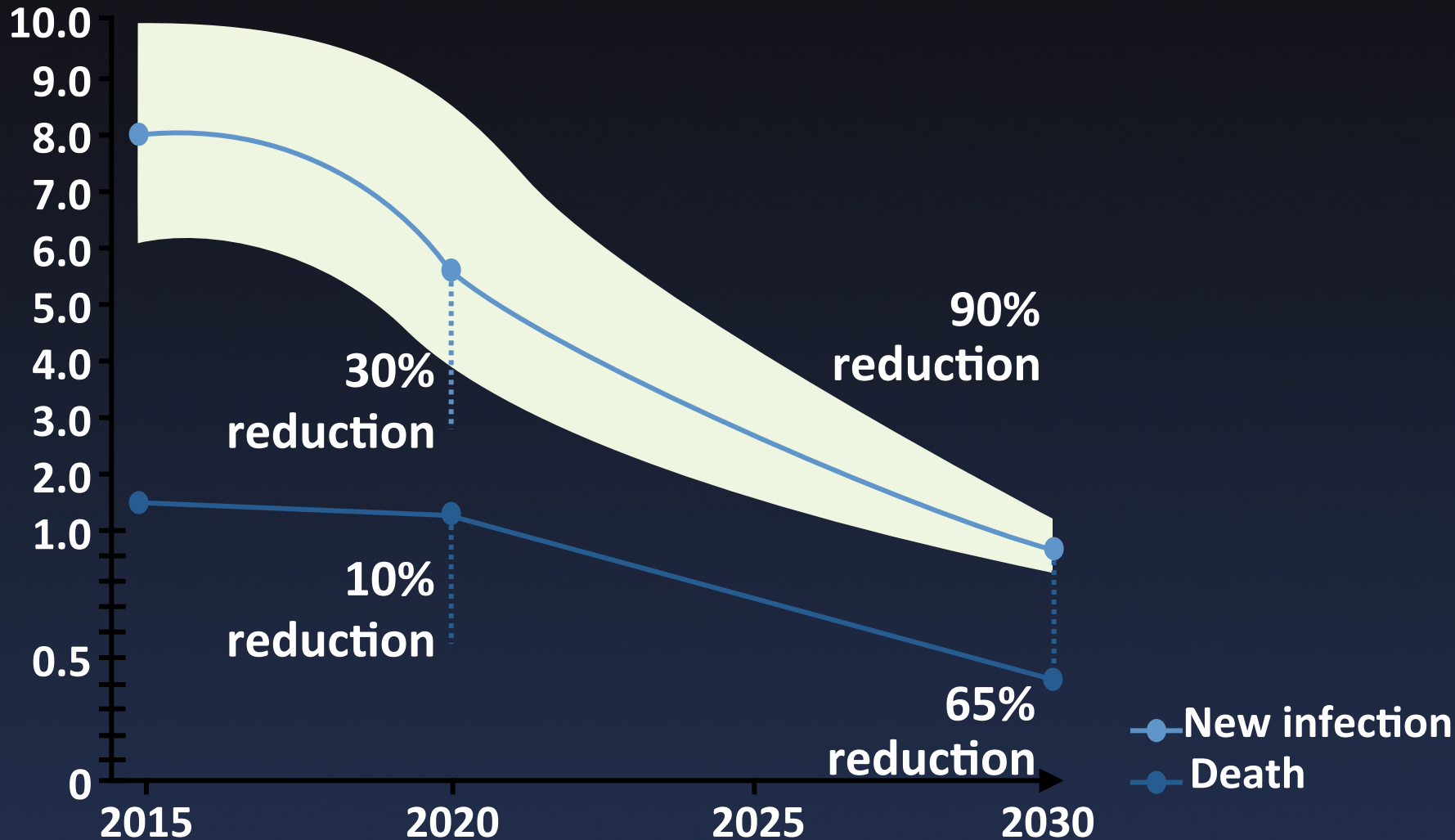
## **Objectives 2030:**

- 90% diagnosed**
- 80% treated**
- 65% reduction in mortality**



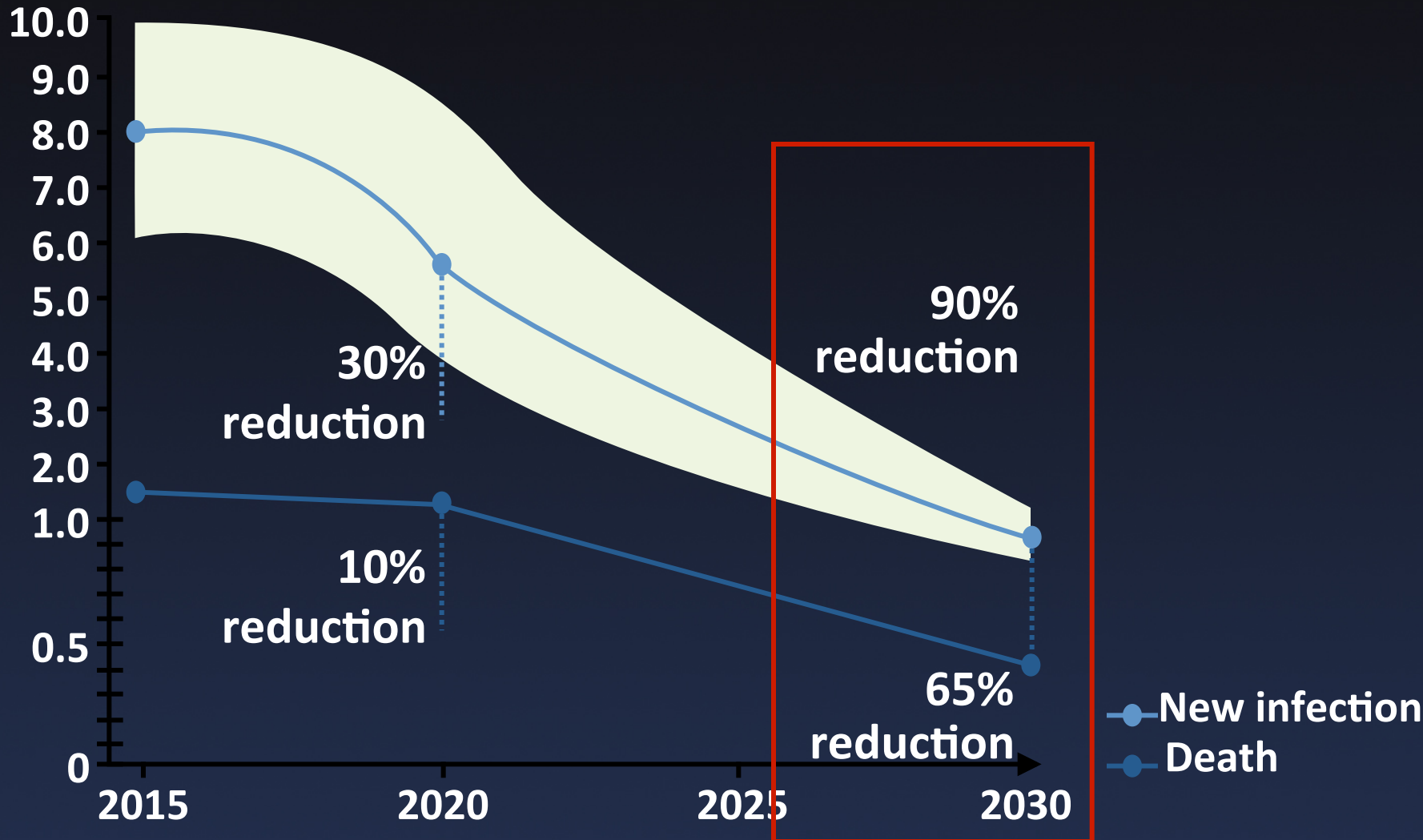
# EU Modelisation

## Reduction of new infections and deaths



# EU Modelisation

## Reduction of new infections and deaths



# Number of patients treated with DAAs 2013-2016

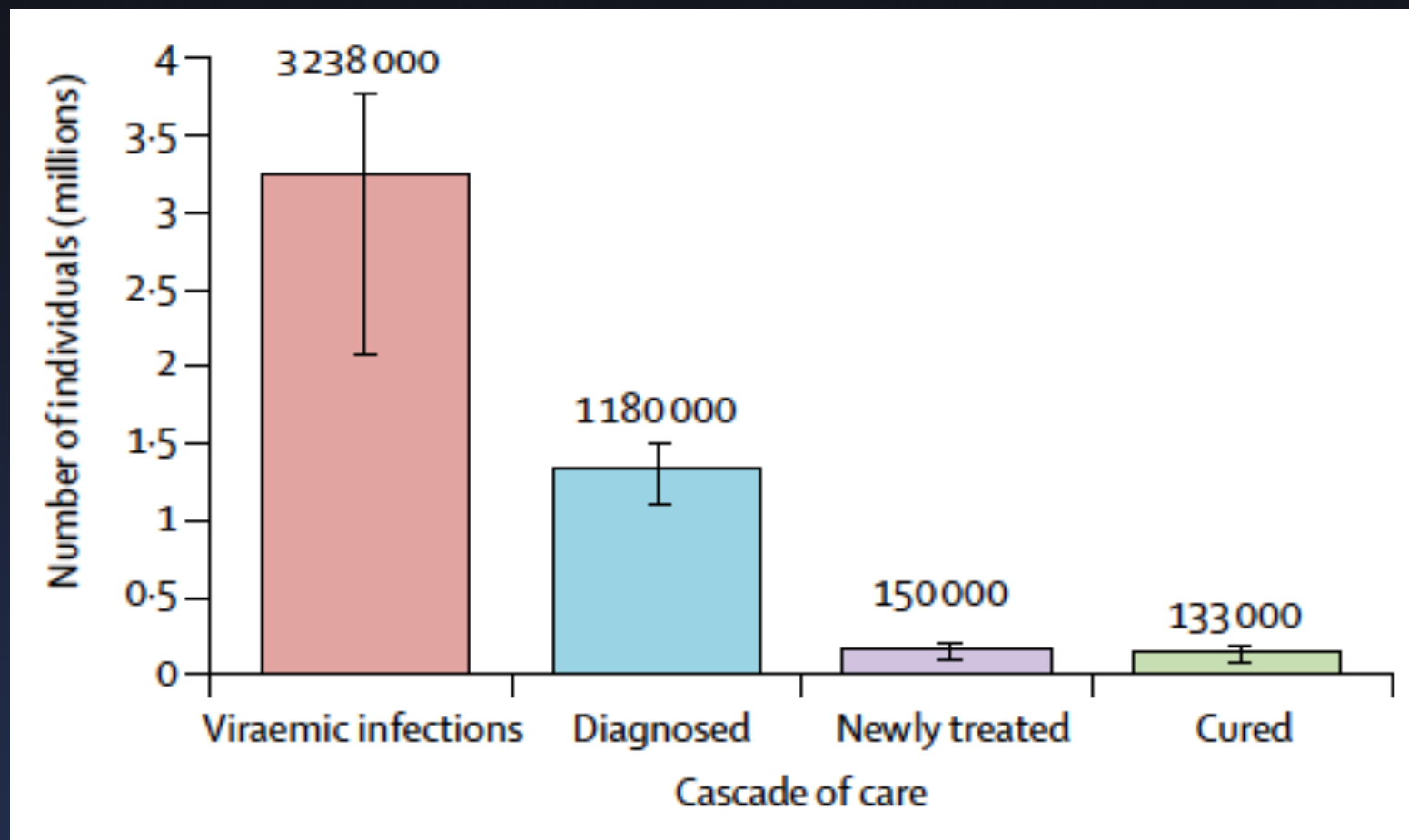
*Conservative estimate of the number of people treated with SOF-based regimens, 2014 to 2016*

	Originator European Union, Japan and USA	Originator ROW	Generic	Total
<b>2013</b>	2 000	0	0	<b>2 000</b>
<b>2014</b>	174 000	15 000	0	<b>189 000</b>
<b>2015</b>	403 000	186 000	157 000	<b>746 000</b>
<b>2016</b>	382 000	118 000	736 000	<b>1 236 000</b>
<b>Total</b>	<b>961 000</b>	<b>319 000</b>	<b>893 000</b>	<b>2 173 000</b>

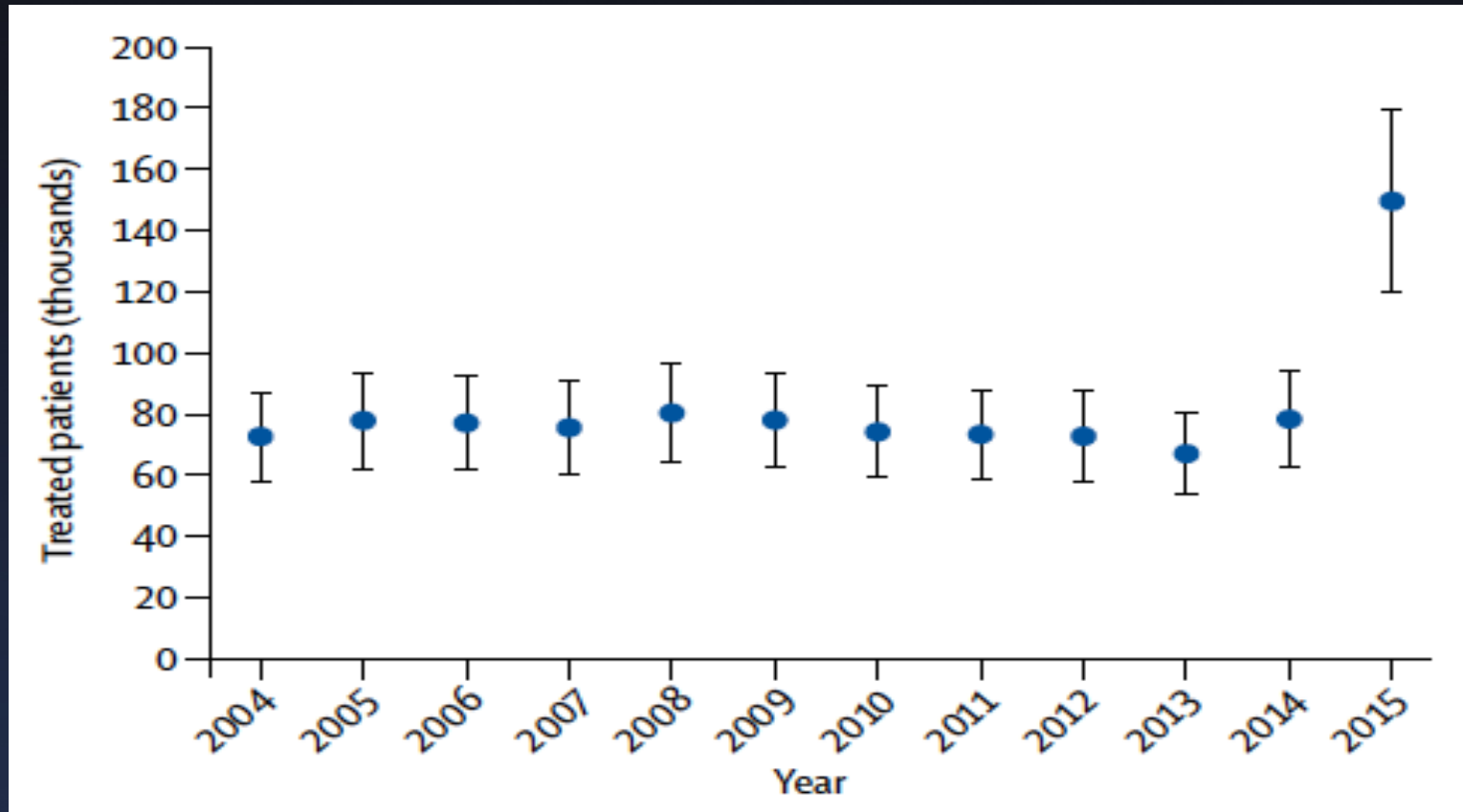
ROW = Rest of the world.

Source of originator data: Gilead. Re generic estimates, see notes for Figure 21.

# Une cascade de soins à améliorer (2015)



# Une cascade de soins à améliorer



# Pourquoi le taux de traitement est-il si bas?

## Patients

- Non connaissance de l'infection → **asymptomatiques**
- Ne veulent pas être traités !
- Traitement est vécu comme « difficile » – même les AVDs

## Médecins

- Faible connaissance de l'hépatite C – Diagnostic et traitement tardifs
  - 57% des MG ne savent pas que l'hépatite C est guérissable !
- Peu de thérapeutes: HGE, infectiologues et internistes

# Challenges

- Le traitement est très efficace et très bien toléré
- Eradication virale très probable
- Elimination possible en théorie mais difficile en pratique...
- Manque de moyens
- Beaucoup reste à faire: dépistage, accès au soins.
- Élargissement des prescripteurs?

**Pas d'élimination sans dépistage large(universel?)  
universel!**

# Initier la dynamique

- Une volonté politique
- Des plans nationaux
- La sensibilisation du public
- La mobilisation de la communauté médicale



HBV

From supression to cure

Innate responses

Adaptive immune responses

**Entryinhibitor**  
• Myrcludex

**Immune Therapies**

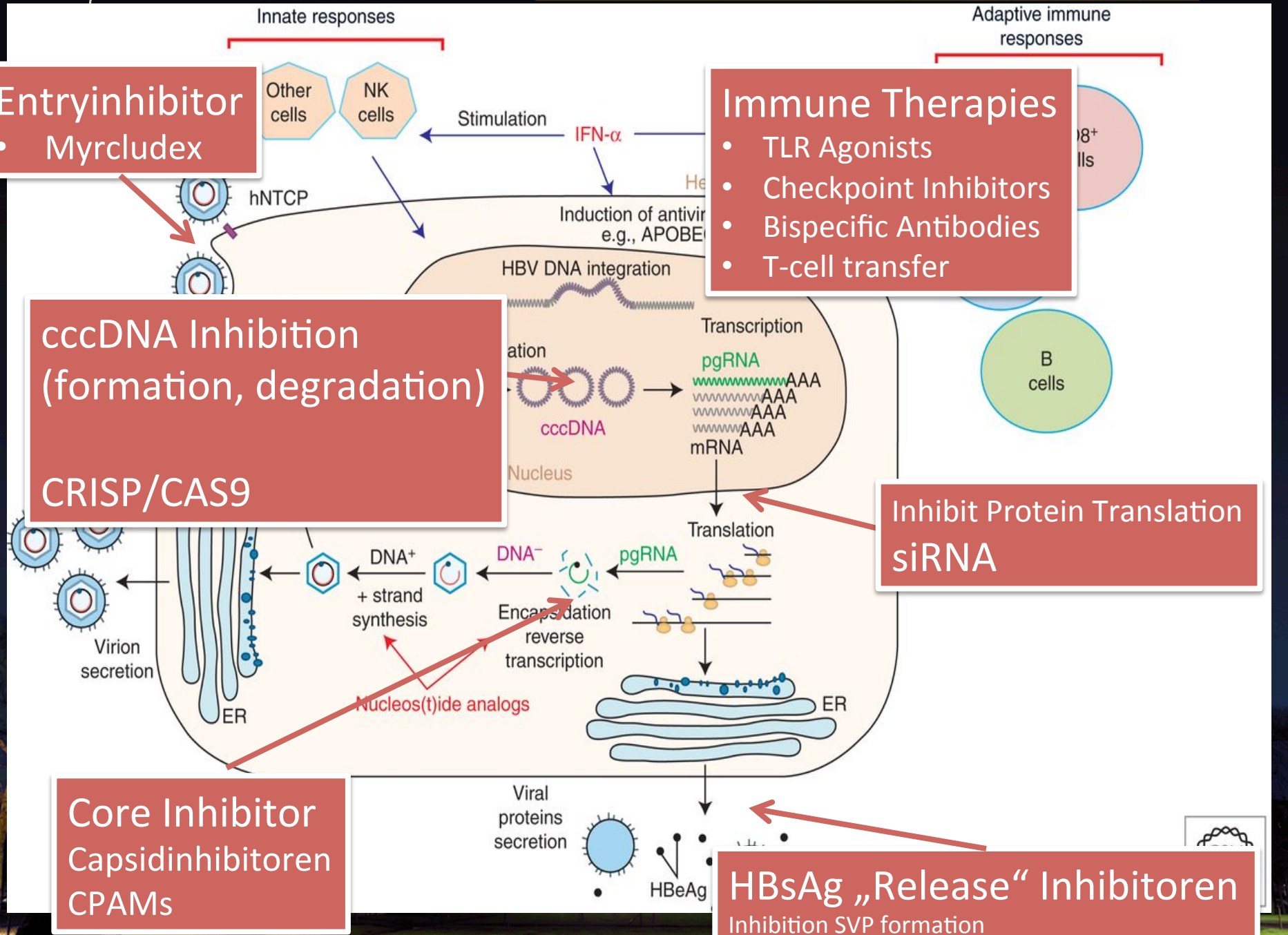
- TLR Agonists
- Checkpoint Inhibitors
- Bispecific Antibodies
- T-cell transfer

**cccDNA Inhibition**  
(formation, degradation)  
**CRISP/CAS9**

**Inhibit Protein Translation**  
**siRNA**

**Core Inhibitor**  
Capsidinhibitoren  
CPAMs

**HBsAg „Release“ Inhibitoren**  
Inhibition SVP formation



# Future Treatment of HBV

Combination available within 3-5 years?

- Potent antiviral
- Inhibitor of viral proteins production (HBs, HBc)
- Restoration of immune response (immuno-modulator)

# Treatment concepts for Hepatitis Delta

Entry inhibitor

*Myrcludex*

Nucleic Acid Polymers

*REP2139 / REP 2165*

Prenylation inhibitor

*Lonafarnib*

Peg-Interferon lambda

Anti-delta+anti-HBV+Peg-Interferon lambda?

NASH

What is the real issue?

# Estimation of the prevalence of NAFLD and NASH in EU and US

	EU	USA	Complication n
NAFLD	116 million (20-30%)	34%	20%
NASH	5%	6 million	10 à 30%

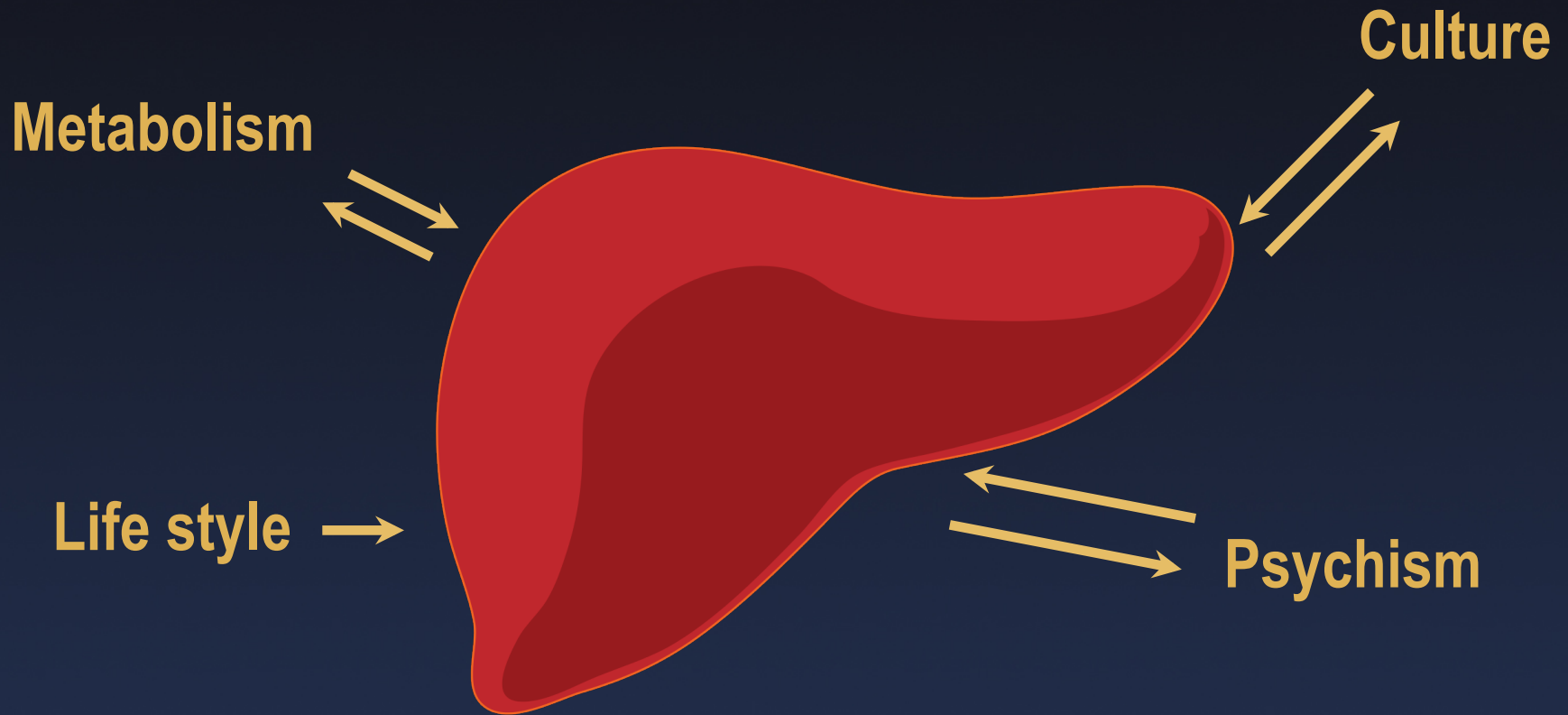
# Global Burden of NAFLD/NASH?

- **Exact prevalence unknown**
- **Increasing prevalence probable**
- **Increasing number of cirrhosis**
- **Increasing number of HCC**
- **Increasing number of LT**

Increasing or/and better recognized?

# CLDs

The result of multiple factors difficult to handle





# Challenges in NASH

Natural history unknown

Physiopathology unknown

Multiple mechanisms involved (metabolism)

Characterization Fatty liver vs NASH difficult: biopsy, no marker

No effective drug available

# The Future of Hepatology

- HCV: good job! Still a long way to go...
- HBV: back to the major global CLD!
- NASH: «emerging» CLD. Facing multiple challenges
- ALD: still a neglected major problem...

CLDs

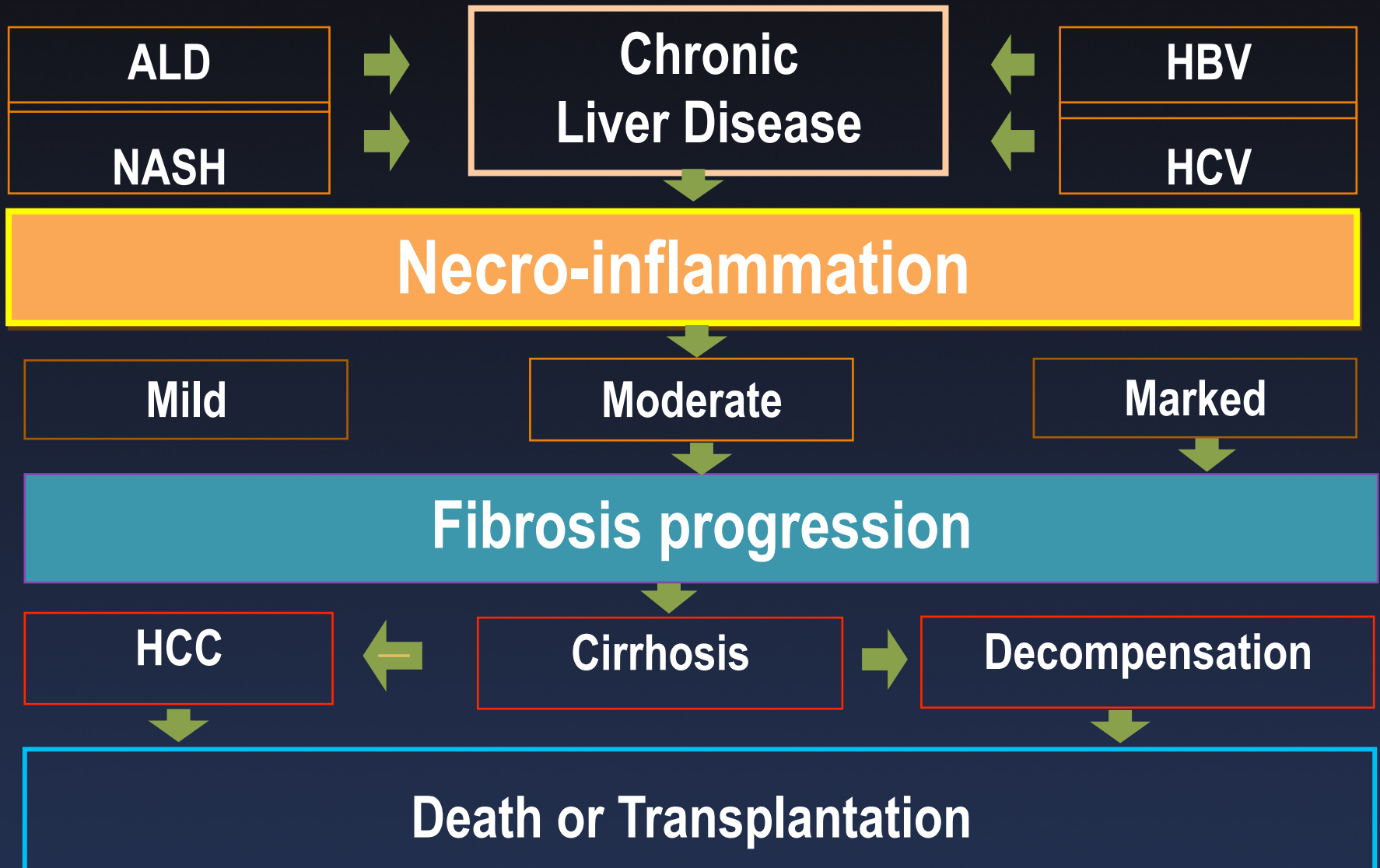
How to Improve  
the Public Health Problem

# Urgent Actions

- Awareness of:
  - Public Health authorities
- Awareness & education of:
  - Physicians
  - Public
- Research on
  - ALD and NASH: need drugs
  - HBV: prevention and drugs
  - Fibrogenesis and INFLAMMATION

# Liver inflammation:

The key mechanism for the progression of CLD



# The Challenges

## Viral CLDs (HBV and HCV)

- Prevention, vaccination
- Screening: majority of patients undiagnosed
- New drugs (combos) to cure HBV
- Access to treatment +++

## “Life style” CLDs (ALD and NASH)

- Awareness
- Screening
- Education
- Research on therapy +++

# The Future of Hepatology

Let's go back from Virology to  
Hepatology and Internal Medicine !

We Won a Battle,  
There are still many battles to come  
But we will win the World War

Charles de Gaulle