# Differential Susceptibility and Infectivity Models. Application to HBV Transmission

G. Sallet [1]

[1]UPVM
IRD (UMI UMMISCO) & INRIA ( EPI MASAIE)

Fields Institute : Theme Weeks on Transmission Heterogeneity

# Plan

# Introduction

Difference in susceptibility is a source of transmission heterogeneity

# Introduction

Difference in susceptibility is a source of transmission heterogeneity
Individuals are not equal in the eyes of an infectious disease :

# Introduction

Difference in susceptibility is a source of transmission heterogeneity
Individuals are not equal in the eyes of an infectious disease :

- Genetic variation of susceptible individuals, difference in behavior, difference in the past history of exposition . . ., many factors may lead to their differentiation of susceptibility on infection.

# Introduction

Difference in susceptibility is a source of transmission heterogeneity
Individuals are not equal in the eyes of an infectious disease :

- Genetic variation of susceptible individuals, difference in behavior, difference in the past history of exposition . . ., many factors may lead to their differentiation of susceptibility on infection.
- The efficacy of available vaccinations for infectious diseases (HBV, measles, . . .) is not perfect. Even if a vaccinated individual may still contract the disease, it is however more protected than a non vaccinated individual

# Introduction

A second source of transmission heterogeneity is the difference in infectivity between individuals

# Introduction

A second source of transmission heterogeneity is the difference in infectivity between individuals

Infectious individual are not equal in transmission :

# Introduction

A second source of transmission heterogeneity is the difference in infectivity between individuals
Infectious individual are not equal in transmission :

- In the studies of the transmission dynamics of HIV, two fundamental hypotheses for variations in infectiousness have been employed (Hyman, Li et al.) :

# Introduction

A second source of transmission heterogeneity is the difference in infectivity between individuals
Infectious individual are not equal in transmission :

- In the studies of the transmission dynamics of HIV, two fundamental hypotheses for variations in infectiousness have been employed (Hyman, Li et al.) :
  - In the staged-progression (SP), initiated by Jacquez, the infected individuals sequentially pass through a series of stages, being highly infectious in the first few weeks after their own infection, then having low infectivity formany years, and finally becoming gradually more infectious as their immune system breaks down and they progress to AIDS

# Introduction

A second source of transmission heterogeneity is the difference in infectivity between individuals
Infectious individual are not equal in transmission :

- In the studies of the transmission dynamics of HIV, two fundamental hypotheses for variations in infectiousness have been employed (Hyman, Li et al.) :
  - In the staged-progression (SP), initiated by Jacquez, the infected individuals sequentially pass through a series of stages, being highly infectious in the first few weeks after their own infection, then having low infectivity formany years, and finally becoming gradually more infectious as their immune system breaks down and they progress to AIDS
  - Another hypothesis is the differential infectivity (DI) hypothesis, where infected individuals enter one of several groups, depending on their infectivity,

# Introduction

Another examples of difference in infectivity between individuals

# Introduction

Another examples of difference in infectivity between individuals

- The so-called asymptomatic carriers

# Introduction

Another examples of difference in infectivity between individuals

- The so-called asymptomatic carriers
- An asymptomatic carrier is an individual that harbor the pathogen of an infectious disease, but who displays no symptoms. However carriers can transmit the infection.

# Introduction

Another examples of difference in infectivity between individuals

- The so-called asymptomatic carriers
- An asymptomatic carrier is an individual that harbor the pathogen of an infectious disease, but who displays no symptoms. However carriers can transmit the infection.
- Typhoid, TB, HBV are example of diseases where asymptomatic carriers play a crucial role.

# Introduction

Since in HBV, the two kind of heterogeneity appear, we will use HBV as a main theme of this talk.

# Plan

# HBV Epidemiology

# HBV Epidemiology

- After contamination, the patient is infected, but does not transmit the disease during 60-90 days

# HBV Epidemiology

- After contamination, the patient is infected, but does not transmit the disease during 60-90 days
- The disease (jaundice) is associated with acute infection and depends on the age.

# HBV Epidemiology

- After contamination, the patient is infected, but does not transmit the disease during 60-90 days
- The disease (jaundice) is associated with acute infection and depends on the age.
  - Jaundice concerns less that 10% of infants aged of 5 years.

# HBV Epidemiology

- After contamination, the patient is infected, but does not transmit the disease during 60-90 days
- The disease (jaundice) is associated with acute infection and depends on the age.
  - Jaundice concerns less that 10% of infants aged of 5 years.
  - concern $30 - 50\%$ of others infants and adults

# HBV Epidemiology

- After contamination, the patient is infected, but does not transmit the disease during 60-90 days
- The disease (jaundice) is associated with acute infection and depends on the age.
  - Jaundice concerns less that 10% of infants aged of 5 years.
  - concern $30 - 50\%$ of others infants and adults
- Most of acute infections lead to complete recovery with immunity.

# HBV Epidemiology

- After contamination, the patient is infected, but does not transmit the disease during 60-90 days
- The disease (jaundice) is associated with acute infection and depends on the age.
  - Jaundice concerns less that 10% of infants aged of 5 years.
  - concern $30 - 50\%$ of others infants and adults
- Most of acute infections lead to complete recovery with immunity.
- However approximatively $30 - 90\%$ of infants and $2 - 10\%$ of infected adults develop a chronic viral infection, which is unnoticed.

# HBV Epidemiology

- After contamination, the patient is infected, but does not transmit the disease during 60-90 days
- The disease (jaundice) is associated with acute infection and depends on the age.
  - Jaundice concerns less that 10% of infants aged of 5 years.
  - concern $30 - 50\%$ of others infants and adults
- Most of acute infections lead to complete recovery with immunity.
- However approximatively $30 - 90\%$ of infants and $2 - 10\%$ of infected adults develop a chronic viral infection, which is unnoticed.
  - Persons with a chronic viral infection to HBV are often asymptomatic.

# HBV Epidemiology

- After contamination, the patient is infected, but does not transmit the disease during 60-90 days
- The disease (jaundice) is associated with acute infection and depends on the age.
  - Jaundice concerns less that 10% of infants aged of 5 years.
  - concern $30 - 50\%$ of others infants and adults
- Most of acute infections lead to complete recovery with immunity.
- However approximatively $30 - 90\%$ of infants and $2 - 10\%$ of infected adults develop a chronic viral infection, which is unnoticed.
  - Persons with a chronic viral infection to HBV are often asymptomatic.
  - They have a high risk of developing a chronic hepatitis and around $15 - 25\%$ will prematurely die of a cirrhosis or a liver cancer (hepatocarcinoma)

# HBV Epidemiology

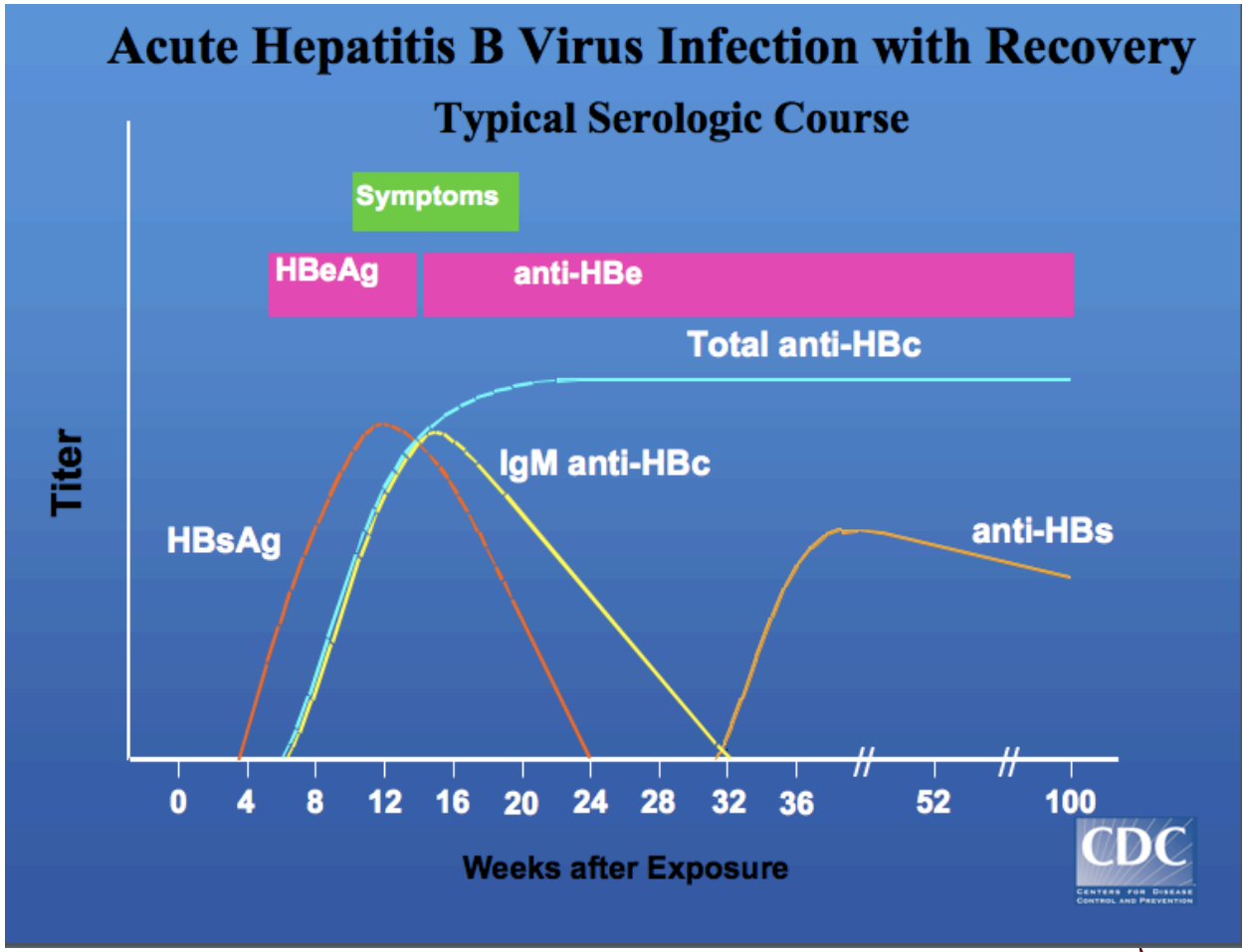
# HBV Epidemiology

Transmission can be perinatal : an infected mother infect his child. Usually by contact of mucous membranes with maternal blood. This is called vertical transmission.

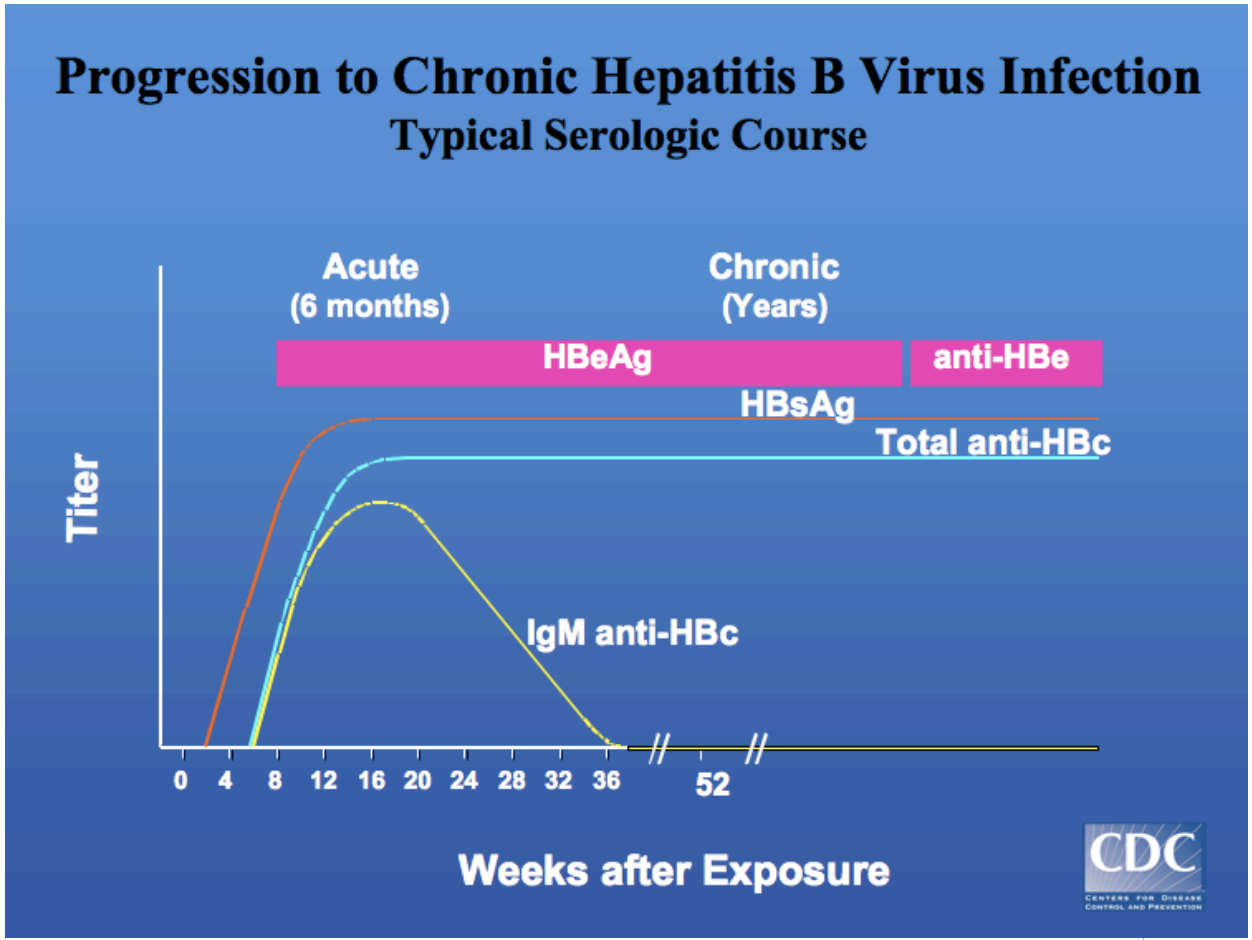
# HBV Epidemiology

Transmission can be perinatal : an infected mother infect his child. Usually by contact of mucous membranes with maternal blood. This is called vertical transmission.
Transmission during the early infancy and infancy is also important in HBV transmission and has significant consequences, as we will see.

# HBV Epidemiology



# HBV Epidemiology



# Plan

# HBV issues

# HBV issues

- Major health problem

# HBV issues

- Major health problem
- It acts as a brake on economic development

# HBV issues

- Major health problem
- It acts as a brake on economic development
- severe disease

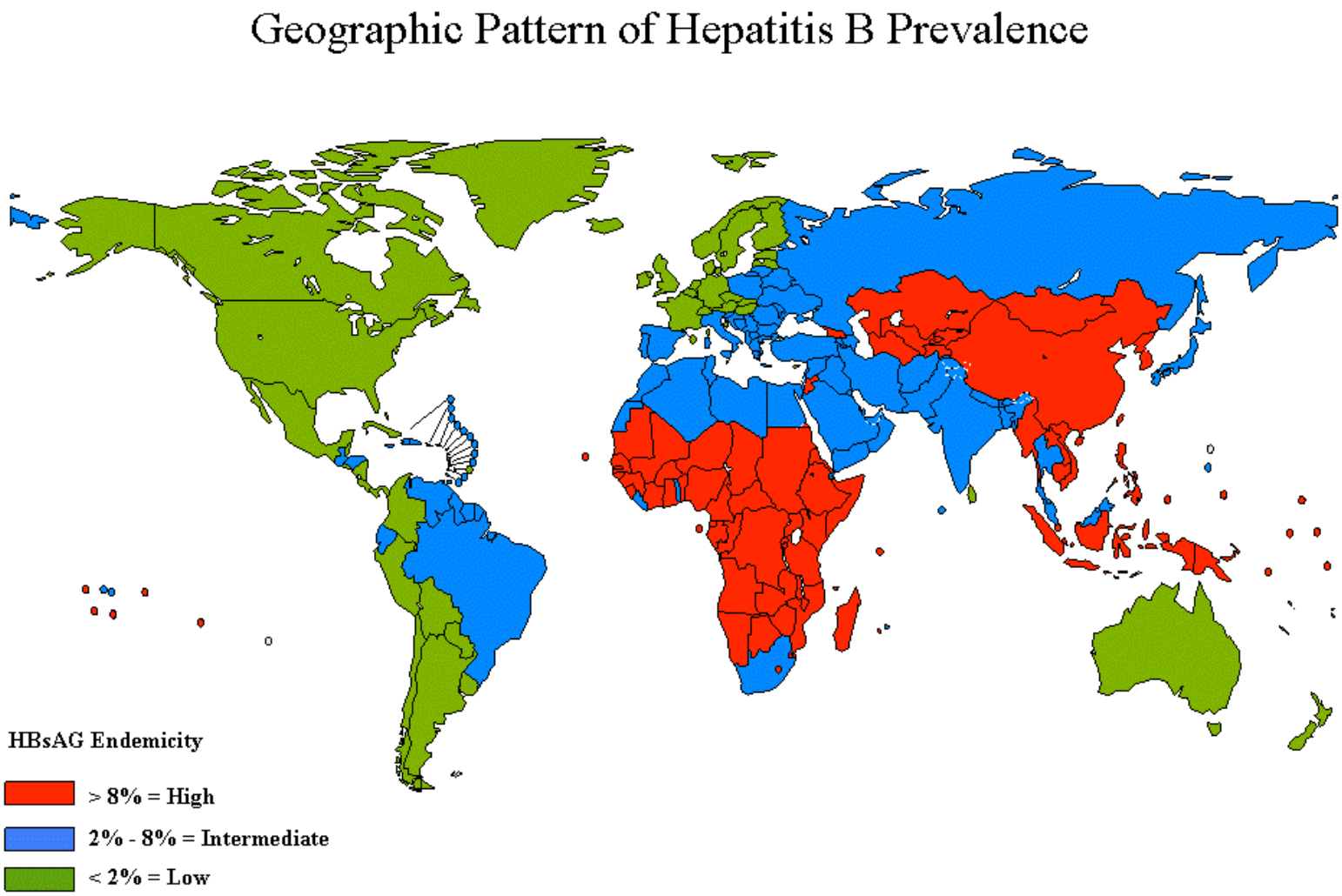
# HBV issues

- Major health problem
- It acts as a brake on economic development
- severe disease
- Treatment is expansive, with limited efficacity

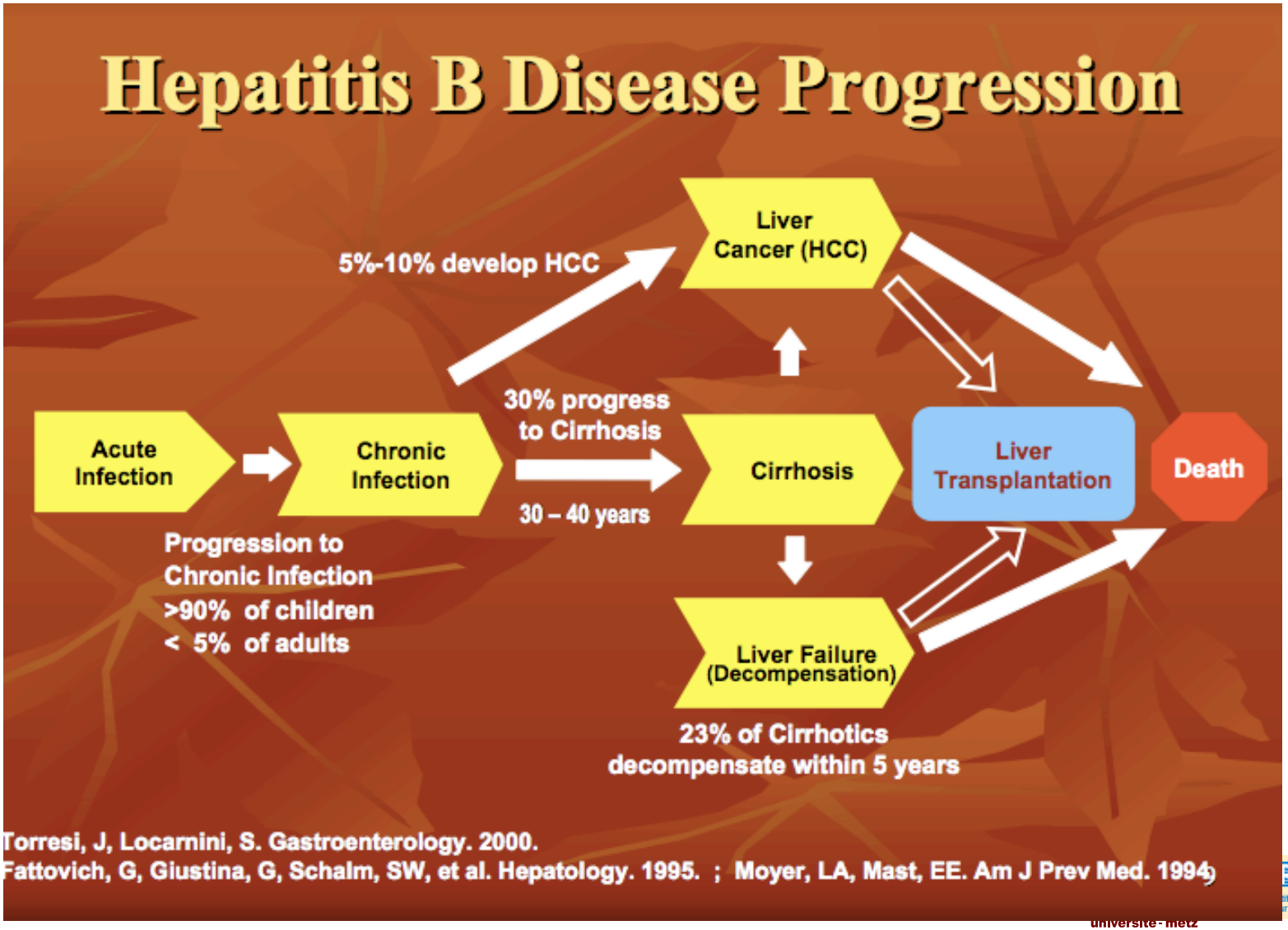
# HBV issues

- Major health problem
- It acts as a brake on economic development
- severe disease
- Treatment is expansive, with limited efficacity
- Efficient measures of prevention : vaccination

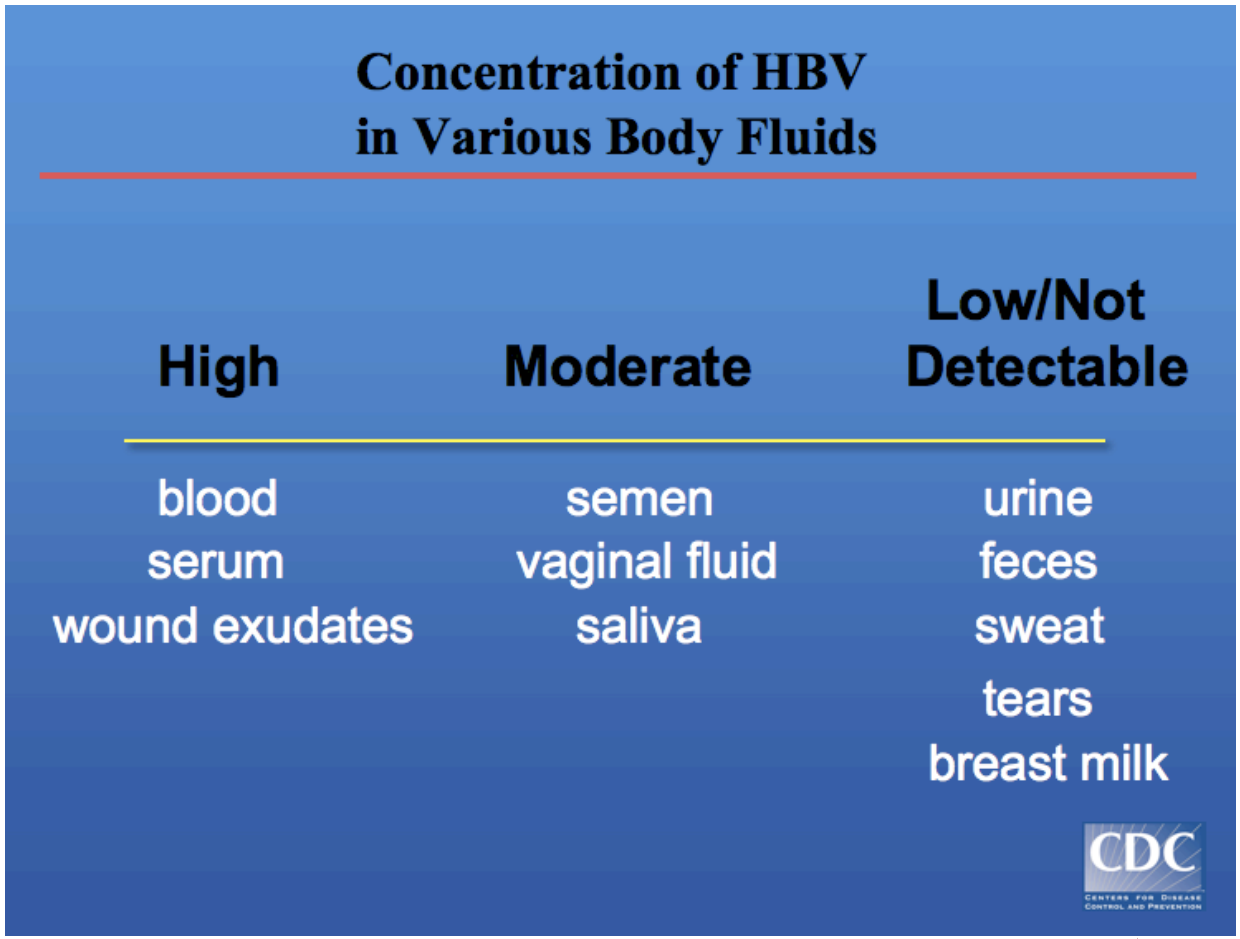
# HBV issues


Geographic Pattern of Hepatitis B Prevalence
HBsAG Endemicity
> 8% = High
2% - 8% = Intermediate
< 2% = Low
Source: WHO data, 1996 (unpublished), Department of Immunization, Vaccines and Biologicals (IVB)
Date of slide: 7 July 2004
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
© WHO 2004. All rights reserved

# HBV issues


Hepatitis B Disease Progression
Liver Cancer (HCC)
5%-10% develop HCC
30% progress to Cirrhosis
Acute Infection
Chronic Infection
Cirrhosis
Liver Transplantation
Death
30 – 40 years
Progression to Chronic Infection
>90% of children
< 5% of adults
Liver Failure (Decompensation)
23% of Cirrhotics decompensate within 5 years
Torresi, J, Locarnini, S. Gastroenterology. 2000.
Fattovich, G, Giustina, G, Schalm, SW, et al. Hepatology. 1995. ; Moyer, LA, Mast, EE. Am J Prev Med. 1994;

# HBV issues


Concentration of HBV
in Various Body Fluids
High
Moderate
Low/Not
Detectable
blood
serum
wound exudates
semen
vaginal fluid
saliva
urine
feces
sweat
tears
breast milk
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

# HBV Epidemiology

# HBV Epidemiology

WHO has proposed different vaccination protocols for Africa and Asia, the two continents concerned in hepatitis B.

# HBV Epidemiology

WHO has proposed different vaccination protocols for Africa and Asia, the two continents concerned in hepatitis B.

The rationale is based on serological studies and the hypothesis that asymptomatic carriers has a high level of HBeAg (Hepatitis B e core antigen)

# HBV Epidemiology

WHO has proposed different vaccination protocols for Africa and Asia, the two continents concerned in hepatitis B.

The rationale is based on serological studies and the hypothesis that asymptomatic carriers has a high level of HBeAg (Hepatitis B e core antigen)

This hypothesis leads to the fact that some authors claims that vertical transmission is negligible in Africa.

# HBV Epidemiology

WHO has proposed different vaccination protocols for Africa and Asia, the two continents concerned in hepatitis B.

The rationale is based on serological studies and the hypothesis that asymptomatic carriers has a high level of HBeAg (Hepatitis B e core antigen)

This hypothesis leads to the fact that some authors claims that vertical transmission is negligible in Africa.

Professor Diallo proves by fine measures that, even if HbeAg level is low in African mothers, in an important part of african mother the viral burden is high. This contradicts the neglibibility of vertical transmission.

# HBV Epidemiology

WHO has proposed different vaccination protocols for Africa and Asia, the two continents concerned in hepatitis B.

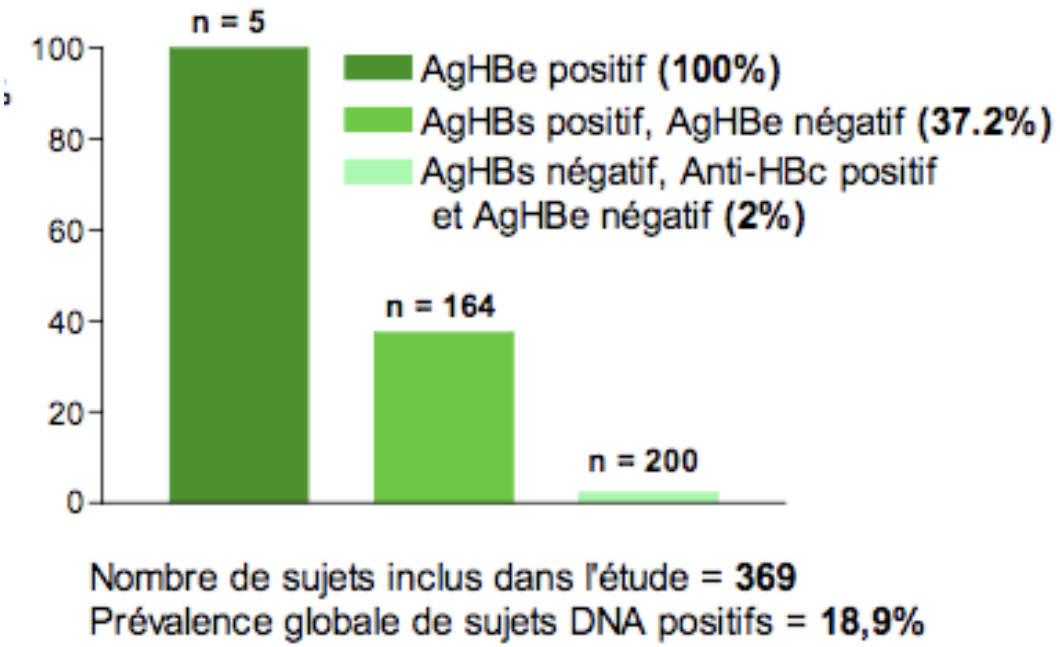
The rationale is based on serological studies and the hypothesis that asymptomatic carriers has a high level of HBeAg (Hepatitis B e core antigen)

This hypothesis leads to the fact that some authors claims that vertical transmission is negligible in Africa.

Professor Diallo proves by fine measures that, even if HbeAg level is low in African mothers, in an important part of african mother the viral burden is high. This contradicts the neglibibility of vertical transmission.
Objective : confirm by modeling the findings of Professor Diallo.

# HBV issues

viral DNA presence



# HBV issues

Conclusion : AgHbe is not a reliable marker of viral activity
vertical transmission is underestimated in Africa

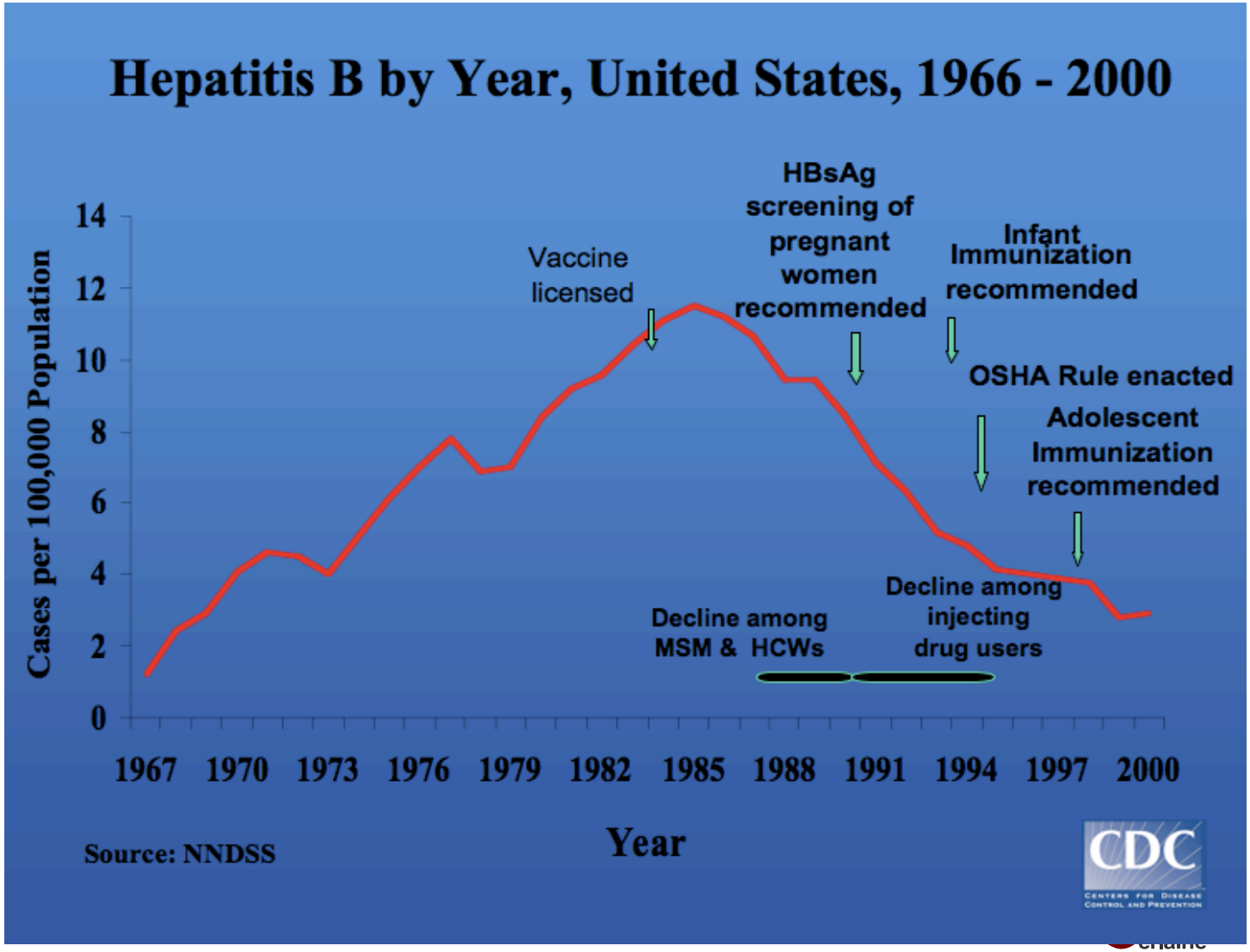
# HBV issues

- Vaccine is highly efficient : 97,2% response

# HBV issues

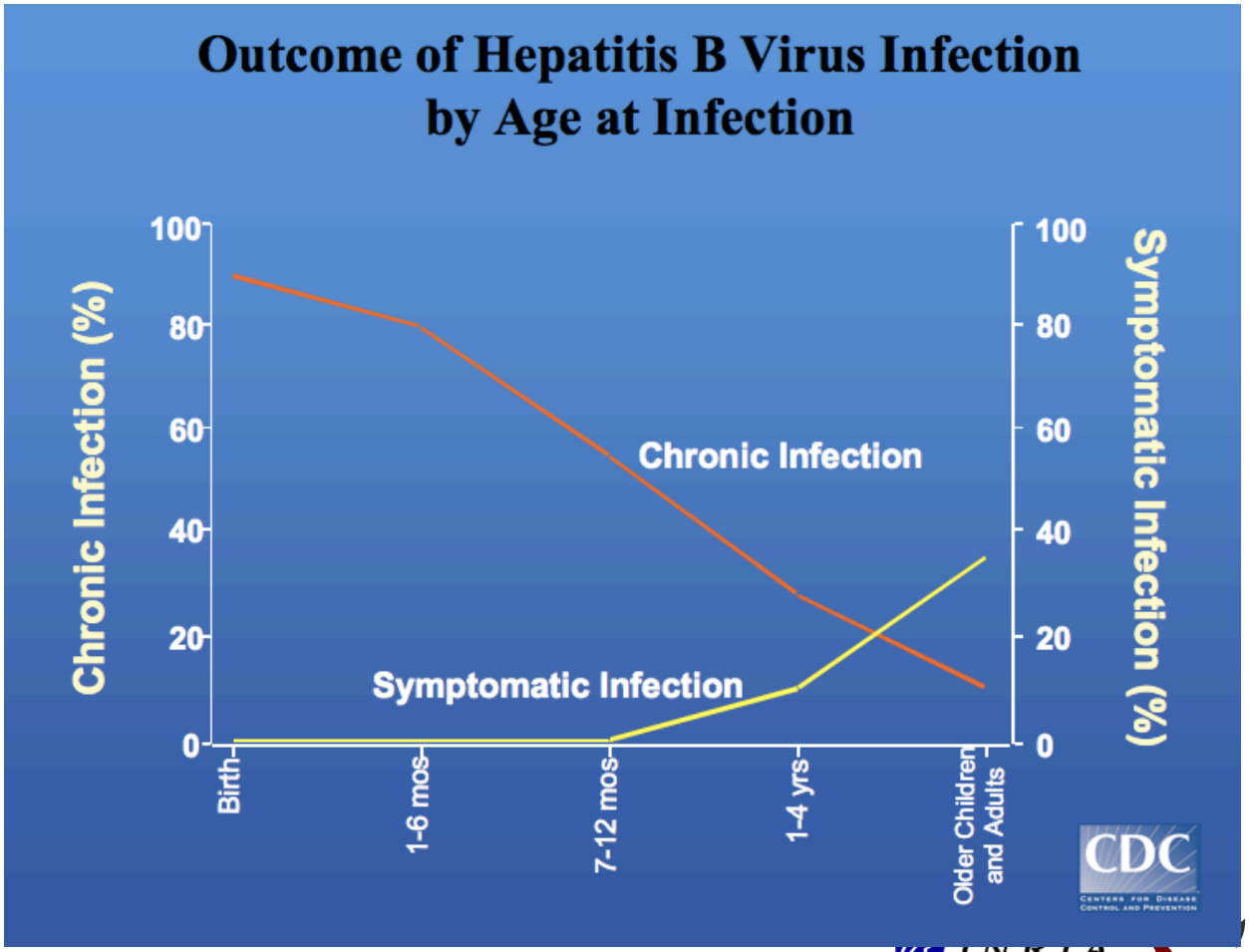
- Vaccine is highly efficient : 97,2% response
- seroprotection 92%

# HBV issues


Hepatitis B by Year, United States, 1966 - 2000
Cases per 100,000 Population
0
2
4
6
8
10
12
14
1967
1970
1973
1976
1979
1982
1985
1988
1991
1994
1997
2000
Year
Vaccine licensed
HBsAg screening of pregnant women recommended
Infant Immunization recommended
OSHA Rule enacted
Adolescent Immunization recommended
Decline among MSM & HCWs
Decline among injecting drug users
Source: NNDSS
CDC
CENTERS FOR DISEASE CONTROL AND PREVENTION

# Evolution to chronicity

% evolution to asymptomatic carrier dependance of age

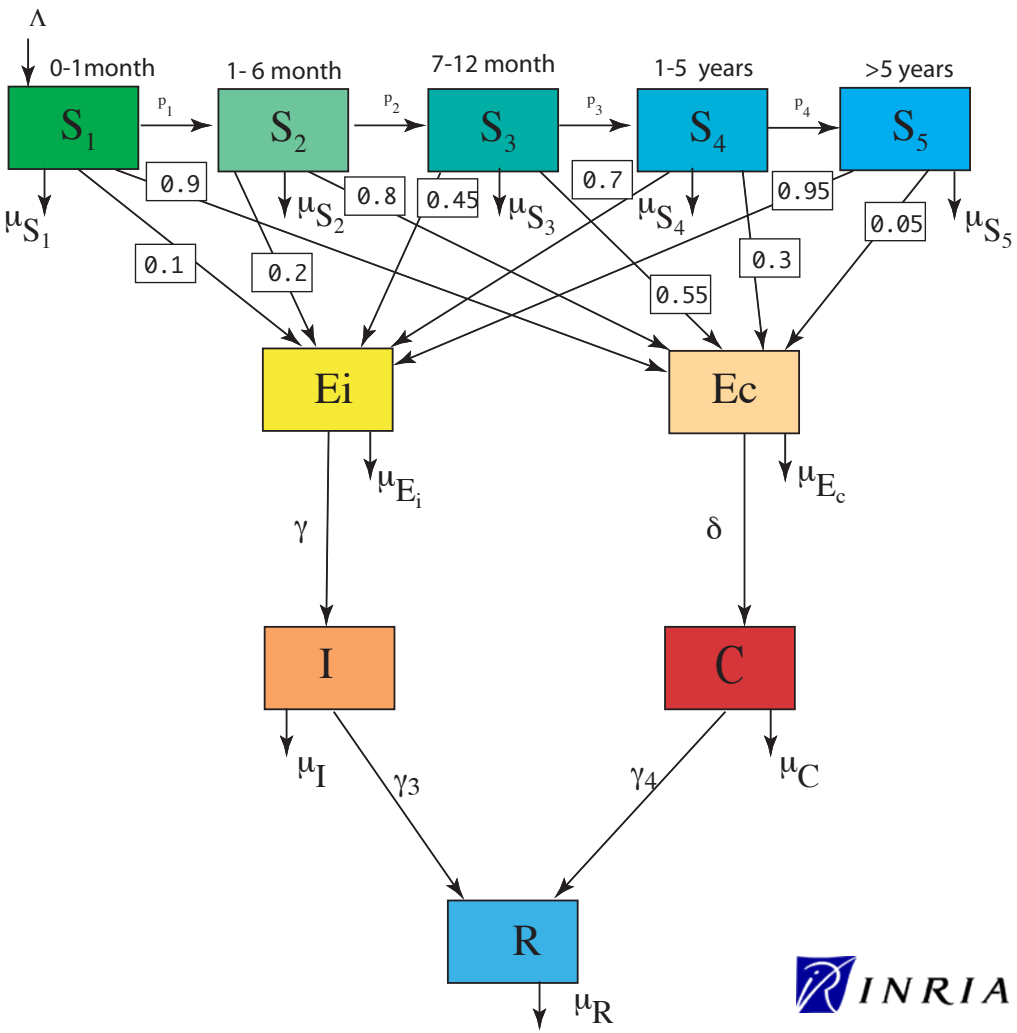


# An HBV transmission model

So we devise the following differential susceptiblity infectivity model :

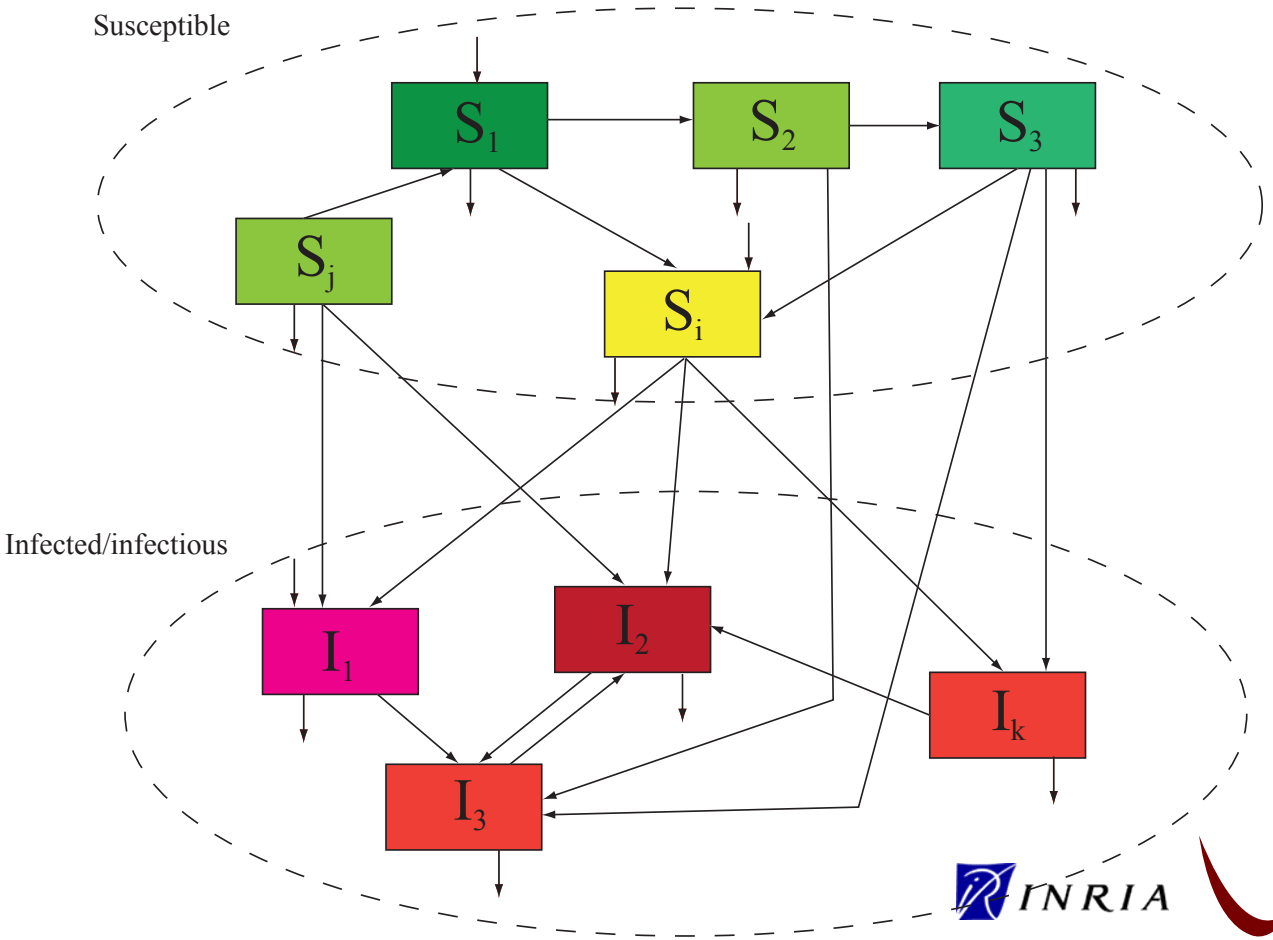
# An HBV transmission model

So we devise the following differential susceptiblity infectivity model :



# General model

The preceding model enters a general class of differential susceptibility and infectivity models :



# General model

This model can be written in a compact ‘vectorial” form

# General model

This model can be written in a compact 'vectorial" form

$$\begin{cases} \dot{S} &= \Lambda - diag(\mu_S)\, S + A_S\, S - diag(B\, I)\, S \\ \dot{I} &= P\, diag(B\, I)\, S - diag(\mu_I + \gamma_I)\, I + A_I\, I, \\ \dot{R} &= L\, I - diag(\mu_R)\, R + A_R\, R \end{cases}$$

# General model

This model can be written in a compact 'vectorial" form

$$\begin{cases} \dot{S} &= \Lambda - diag(\mu_S)\, S + A_S\, S - diag(B\, I)\, S \\ \dot{I} &= P\, diag(B\, I)\, S - diag(\mu_I + \gamma_I)\, I + A_I\, I, \\ \dot{R} &= L\, I - diag(\mu_R)\, R + A_R\, R \end{cases}$$

$B$ is the WAIFW matrix (Who Acquires Infection From Whom matrix )

# General model

This model can be written in a compact 'vectorial" form

$$\begin{cases} \dot{S} &= \Lambda - diag(\mu_S)\, S + A_S\, S - diag(B\, I)\, S \\ \dot{I} &= P\, diag(B\, I)\, S - diag(\mu_I + \gamma_I)\, I + A_I\, I, \\ \dot{R} &= L\, I - diag(\mu_R)\, R + A_R\, R \end{cases}$$

$B$ is the WAIFW matrix (Who Acquires Infection From Whom matrix )
$P$ is the distribution of the susceptible which are infected in the infectious compartments. This a column sum stochastic matrix.

# General model

Since the model is in triangular form, by a Vidyasagar result, for studying stability we just have to consider

# General model

Since the model is in triangular form, by a Vidyasagar result, for studying stability we just have to consider

$$\begin{cases} \dot{S} &= \Lambda - diag(\mu_S)\, S + A_S\, S - diag(B\, I)\, S \\ \dot{I} &= P\, diag(B\, I)\, S - diag(\mu_I + \gamma_I)\, I + A_I\, I, \end{cases}$$

# General model

We have the following natural hypotheses

**H1** Any "susceptible" compartment is accessible from a "susceptible" compartment with recruitment.

# General model

We have the following natural hypotheses

**H1** Any "susceptible" compartment is accessible from a "susceptible" compartment with recruitment.

**H2** : Any infected-infectious compartment is accessible from at least one compartment which is an "entry-point" for infection.
An entry-point compartment for infection is an infected-infectious compartment with an edge coming from the susceptible compartments.
Equivalently this is the compartment with index for which the components of $P\mathbb{1}$ are positive.

# General model

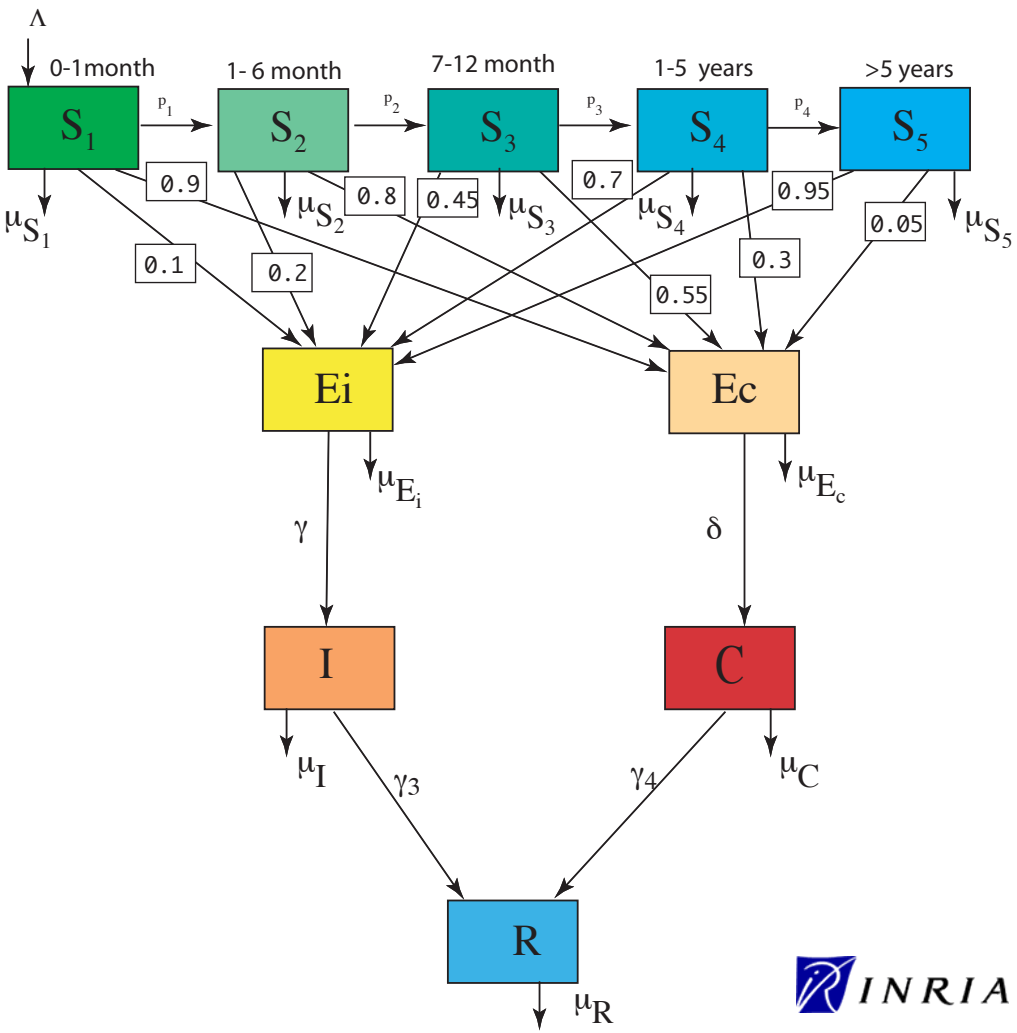
We have the following natural hypotheses

**H1** Any "susceptible" compartment is accessible from a "susceptible" compartment with recruitment.

**H2** : Any infected-infectious compartment is accessible from at least one compartment which is an "entry-point" for infection.
An entry-point compartment for infection is an infected-infectious compartment with an edge coming from the susceptible compartments.
Equivalently this is the compartment with index for which the components of $P\mathbb{1}$ are positive.
We formulate these hypotheses, to prevent a compartment to be asymptotically emptied. Since we are looking for the asymptotic behavior these hypotheses does not reduce the generality of our model.

# HBV model

It is straightforward to check the two hypotheses on our HBV model :



# General model

To summarize, the characteristics of our general model are :

# General model

To summarize, the characteristics of our general model are :

- We use bilinear mass action transmission ;

# General model

To summarize, the characteristics of our general model are :

- We use bilinear mass action transmission ;
- No recruitment in the infected/infectious compartments ;

# General model

To summarize, the characteristics of our general model are :

- We use bilinear mass action transmission ;
- No recruitment in the infected/infectious compartments ;
- No flows from the infected/ infectious towards the susceptible compartments ;

# General model

To summarize, the characteristics of our general model are :

- We use bilinear mass action transmission ;
- No recruitment in the infected/infectious compartments ;
- No flows from the infected/ infectious towards the susceptible compartments ;
- Hypotheses to guarantee that no compartment can be asymptotically emptied.

# General model

To summarize, the characteristics of our general model are :

- We use bilinear mass action transmission ;
- No recruitment in the infected/infectious compartments ;
- No flows from the infected/ infectious towards the susceptible compartments ;
- Hypotheses to guarantee that no compartment can be asymptotically emptied.

**Remark** We introduce perinatal transmission by creating compartments of immediate newborns and early infancy. Transmission in HBV is not *in utero* but begins with delivery and later.

# General model

Within this framework we have the following result

**Theorem**

*Whe set*

$$A = -diag(\mu_I + \gamma_I) + A_I.$$

*Then*

- *If $B$ is a rank one matrix, i.e., $B = \alpha\,\beta^T$ then*

$$\mathcal{R}_0 = \left\langle \beta \,\middle|\, (-A^{-1})\, P\, diag(\alpha)\, S^\star \right\rangle$$

- *If $P$ is a rank one matrix, i.e., $P = p\,\mathbb{1}^T$*

$$\mathcal{R}_0 = \langle B\,(-A^{-1})\,p \mid S^* \rangle.$$

# General model

If $P$ or $B$ are rank one matrices we have

**Theorem**

*If $\mathcal{R}_0 \leq 1$ then the DFE of the system is globally asymptotically stable on the nonnegative orthant.*

# General model

If $P$ or $B$ are rank one matrices we have

**Theorem**

*If $\mathcal{R}_0 \leq 1$ then the DFE of the system is globally asymptotically stable on the nonnegative orthant.*

*If $\mathcal{R}_0 > 1$ the DFE is unstable.*

# General model

If $P$ or $B$ are rank one matrices we have

**Theorem**

*If $\mathcal{R}_0 \leq 1$ then the DFE of the system is globally asymptotically stable on the nonnegative orthant.*

*If $\mathcal{R}_0 > 1$ the DFE is unstable.*

*There exists a unique endemic equilibrium in the nonnegative orthant, for the system if and only if $\mathcal{R}_0 > 1$.*

# Sketch of proof

**First step** For any $\varepsilon > 0$, The subset $K_\varepsilon$ of the nonnegative orthant $\mathbb{R}^n_+ \times \mathbb{R}^m_+$, defined by

$$K_\varepsilon = \left\{ (S, I) \,\middle|\, S \geq 0 \;\; ; I \geq 0 \;\; ; N \leq (\langle \Lambda | \mathbb{1} \rangle + \varepsilon)/\mu_o \right\},$$

is a positively invariant compact absorbing set

# Sketch of proof

**First step** For any $\varepsilon > 0$, The subset $K_\varepsilon$ of the nonnegative orthant $\mathbb{R}^n_+ \times \mathbb{R}^m_+$, defined by

$$K_\varepsilon = \left\{ (S, I) \,\middle|\, S \geq 0 \;\; ; I \geq 0 \;\; ; N \leq (\langle \Lambda | \mathbb{1} \rangle + \varepsilon)/\mu_o \right\},$$

is a positively invariant compact absorbing set

**Second step**

The set $\Omega$ defined by

$$\Omega = \left\{ (S, I) \in K_\varepsilon \,\middle|\, S \leq S^* \right\},$$

is a positively invariant compact set for system

# Sketch of proof

**Third step**

The DFE is $(S^*, 0)$ with $S^* = -\left(\text{diag}(-\mu_S) + A_S\right)^{-1} \Lambda \gg 0$.

# Sketch of proof

**Third step**

The DFE is $(S^*, 0)$ with $S^* = -\left(\text{diag}(-\mu_S) + A_S\right)^{-1} \Lambda \gg 0$.

The positivity comes from the accessibility of any susceptible compartment.

# Sketch of proof

**Third step**
The DFE is $(S^*, 0)$ with $S^* = -\left(\mathrm{diag}(-\mu_S) + A_S\right)^{-1} \Lambda \gg 0$.
The positivity comes from the accessibility of any susceptible compartment.

**Fourth step** For the case of rank one $B$, we use on $\Omega$ the LaSalle function

$$V(S, I) = \langle \beta | - A^{-1} I \rangle$$

# Sketch of proof

**Third step**
The DFE is $(S^*, 0)$ with $S^* = -\left(\mathrm{diag}(-\mu_S) + A_S\right)^{-1} \Lambda \gg 0$.
The positivity comes from the accessibility of any susceptible compartment.

**Fourth step** For the case of rank one $B$, we use on $\Omega$ the LaSalle function

$$V(S, I) = \langle \beta | - A^{-1} I \rangle$$

It is easy to see that $\dot{V} \leq \langle \beta | I \rangle (\mathcal{R}_0 - 1) \leq 0$

# Sketch of proof

**Third step**
The DFE is $(S^*, 0)$ with $S^* = -\left(\mathrm{diag}(-\mu_S) + A_S\right)^{-1} \Lambda \gg 0$.
The positivity comes from the accessibility of any susceptible compartment.

**Fourth step** For the case of rank one $B$, we use on $\Omega$ the LaSalle function

$$V(S, I) = \langle \beta | - A^{-1} I \rangle$$

It is easy to see that $\dot{V} \leq \langle \beta | I \rangle (\mathcal{R}_0 - 1) \leq 0$
By Lasalle we conclude to the global stability on $\Omega$.

# Sketch of proof

**Third step**
The DFE is $(S^*, 0)$ with $S^* = -\left(\mathrm{diag}(-\mu_S) + A_S\right)^{-1} \Lambda \gg 0$.
The positivity comes from the accessibility of any susceptible compartment.

**Fourth step** For the case of rank one $B$, we use on $\Omega$ the LaSalle function

$$V(S, I) = \langle \beta | - A^{-1} I \rangle$$

It is easy to see that $\dot{V} \leq \langle \beta | I \rangle (\mathcal{R}_0 - 1) \leq 0$
By Lasalle we conclude to the global stability on $\Omega$. Then we show the attractivity on $K_\varepsilon \setminus \Omega$.

# Sketch of proof

**Third step**
The DFE is $(S^*, 0)$ with $S^* = -\left(\mathrm{diag}(-\mu_S) + A_S\right)^{-1} \Lambda \gg 0$.
The positivity comes from the accessibility of any susceptible compartment.

**Fourth step** For the case of rank one $B$, we use on $\Omega$ the LaSalle function

$$V(S, I) = \langle \beta | - A^{-1} I \rangle$$

It is easy to see that $\dot{V} \leq \langle \beta | I \rangle (\mathcal{R}_0 - 1) \leq 0$
By Lasalle we conclude to the global stability on $\Omega$. Then we show the attractivity on $K_\varepsilon \setminus \Omega$. Since $K_\varepsilon$ is absorbing the proof is finished.
The case for rank one $P$ is similar.

# Sketch of proof

Uniqueness of the EE : case rank one $B = \alpha \beta^T$

# Sketch of proof

Uniqueness of the EE : case rank one $B = \alpha\,\beta^T$
The endemic equilibrium $(\bar{S}, \bar{I})$ satisfies

$$\begin{aligned} \bar{S} = & \quad -\left[-\mathrm{diag}(\mu_S) - \langle \beta | \bar{I} \rangle\, \mathrm{diag}(\alpha) + A_S\right]^{-1} \Lambda \\ = & \quad -M(\langle \beta \mid \bar{I} \rangle)^{-1}\, \Lambda. \end{aligned}$$

# Sketch of proof

Uniqueness of the EE : case rank one $B = \alpha\,\beta^T$
The endemic equilibrium $(\bar{S}, \bar{I})$ satisfies

$$\begin{aligned} \bar{S} = & -\left[-\mathrm{diag}(\mu_S) - \langle\beta|\bar{I}\rangle\,\mathrm{diag}(\alpha) + A_S\right]^{-1}\Lambda \\ = & -M(\langle\beta \mid \bar{I}\rangle)^{-1}\,\Lambda. \end{aligned}$$

Where have set

$$M(x) = -\mathrm{diag}\left(\mu_S + x\,\alpha\right)) + A_S,$$

# Sketch of proof

Uniqueness of the EE : case rank one $B = \alpha\,\beta^T$
The endemic equilibrium $(\bar{S}, \bar{I})$ satisfies

$$\begin{aligned} \bar{S} = & -\left[-\mathrm{diag}(\mu_S) - \langle\beta|\bar{I}\rangle\,\mathrm{diag}(\alpha) + A_S\right]^{-1}\Lambda \\ = & -M(\langle\beta \mid \bar{I}\rangle)^{-1}\,\Lambda. \end{aligned}$$

Where have set

$$M(x) = -\mathrm{diag}\left(\mu_S + x\,\alpha\right)) + A_S,$$

and

$$\bar{I} = \langle\beta \mid \bar{I}\rangle\,(-A^{-1})\,P\,\mathrm{diag}(\alpha)\,\bar{S}.$$

# Sketch of proof

Then it is sufficient to determine $\langle \beta \mid \bar{I} \rangle$ to compute $(\bar{S}, \bar{I})$.

# Sketch of proof

Then it is sufficient to determine $\langle \beta \mid \bar{I} \rangle$ to compute $(\bar{S}, \bar{I})$.
We have the realtion

$$\left\langle \beta \left| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[ -M(\langle \beta \mid \bar{I} \rangle)^{-1} \right] \Lambda \right\rangle = 1.$$

# Sketch of proof

Then it is sufficient to determine $\langle \beta \mid \bar{I} \rangle$ to compute $(\bar{S}, \bar{I})$.
We have the realtion

$$\left\langle \beta \middle| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[-M(\langle \beta \mid \bar{I} \rangle)^{-1}\right]\, \Lambda \right\rangle = 1.$$

In other words the scalar $\langle \beta \mid \bar{I} \rangle$ is a solution of $H(x) = 1$ with

$$H(x) = \left\langle \beta \middle| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[-M(x)^{-1}\right]\, \Lambda \right\rangle.$$

# Sketch of proof

Then it is sufficient to determine $\langle \beta \mid \bar{I} \rangle$ to compute $(\bar{S}, \bar{I})$.
We have the realtion

$$\left\langle \beta \middle| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[ -M(\langle \beta \mid \bar{I} \rangle)^{-1} \right] \Lambda \right\rangle = 1.$$

In other words the scalar $\langle \beta \mid \bar{I} \rangle$ is a solution of $H(x) = 1$ with

$$H(x) = \left\langle \beta \middle| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[ -M(x)^{-1} \right] \Lambda \right\rangle.$$

It is not difficult to show that $H(x)$ is strictly decreasing function.

# Sketch of proof

Then it is sufficient to determine $\langle \beta \mid \bar{I} \rangle$ to compute $(\bar{S}, \bar{I})$.
We have the realtion

$$\left\langle \beta \middle| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[-M(\langle \beta \mid \bar{I} \rangle)^{-1}\right]\, \Lambda \right\rangle = 1.$$

In other words the scalar $\langle \beta \mid \bar{I} \rangle$ is a solution of $H(x) = 1$ with

$$H(x) = \left\langle \beta \middle| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[-M(x)^{-1}\right]\, \Lambda \right\rangle.$$

It is not difficult to show that $H(x)$ is strictly decreasing function.
Moreover $H(x)$ satisfies $\lim_{x \to +\infty} H(x) = 0$.

# Sketch of proof

Then it is sufficient to determine $\langle \beta \mid \bar{I} \rangle$ to compute $(\bar{S}, \bar{I})$.
We have the realtion

$$\left\langle \beta \middle| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[-M(\langle \beta \mid \bar{I} \rangle)^{-1}\right]\, \Lambda \right\rangle = 1.$$

In other words the scalar $\langle \beta \mid \bar{I} \rangle$ is a solution of $H(x) = 1$ with

$$H(x) = \left\langle \beta \middle| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[-M(x)^{-1}\right]\, \Lambda \right\rangle.$$

It is not difficult to show that $H(x)$ is strictly decreasing function. Moreover $H(x)$ satisfies $\lim_{x \to +\infty} H(x) = 0$. Then a unique positive solution exists if and only if $H(0) > 1$.

# Sketch of proof

Then it is sufficient to determine $\langle \beta \mid \bar{I} \rangle$ to compute $(\bar{S}, \bar{I})$.
We have the realtion

$$\left\langle \beta \middle| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[-M(\langle \beta \mid \bar{I} \rangle)^{-1}\right]\, \Lambda \right\rangle = 1.$$

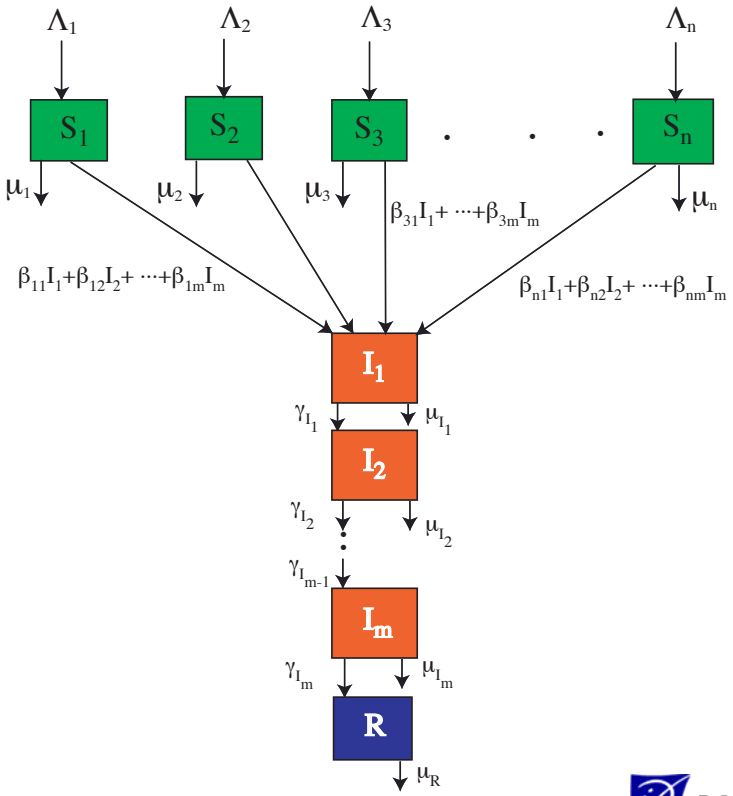
In other words the scalar $\langle \beta \mid \bar{I} \rangle$ is a solution of $H(x) = 1$ with

$$H(x) = \left\langle \beta \middle| (-A^{-1})\, P\, \mathrm{diag}(\alpha)\, \left[-M(x)^{-1}\right]\, \Lambda \right\rangle.$$

It is not difficult to show that $H(x)$ is strictly decreasing function. Moreover $H(x)$ satisfies $\lim_{x \to +\infty} H(x) = 0$. Then a unique positive solution exists if and only if $H(0) > 1$. Since $H(0) = \mathcal{R}_0$ we have a unique positive solution.

# A global stability result for the endemic equilibrium

The question of the stability of the endemic equilibrium is difficult. For example consider the following DIDS model (generalizing a Hyman-Li et al. model)



# A stability result for the endemic equilibrium

For this model the endemic equilibrium is GAS iff $\mathcal{R}_0 > 1$
We use the following Volterra Lyapunov function

$$V_{EE}(S, I) = \left\langle S - \bar{S} \ln S \,|\mathbb{1}\right\rangle + \left\langle B(-A^{-1}) \left(I - \mathrm{diag}(\bar{I}) \ln I\right) |\bar{S}\right\rangle - K.$$

# General model

A simulation with perinatal transmission ( Sénégal data )