Chronic Hepatitis B
What every GP should know

Prof Ed Gane
NZ Liver Unit

Case 1

- 55 Yr old Tonga male
  - »Well but dad died of liver cancer
  - »LFTs: **ALT 85**, GGT 60; ALP 75; bilirubin 12

What next?

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  - »LFTs: **ALT 85**, GGT 60; ALP 75; bilirubin 12
- HBsAg +
- HBeAg neg

What next?

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- **HBV DNA 6,500,000 IU/mL**

What next?

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  - »LFTs: **ALT 85**, GGT 60; ALP 75; bilirubin 12
- HBsAg +
- HBeAg neg
- **HBV DNA 6,500,000 IU/mL**
- **Referred to Hospital**
- **Fibroscan ➡ cirrhosis**

Treat?

Case 2

- 35 Yr old European male
  - 2 weeks malaise, anorexia
  - Now dark urine, RUQ abdo pain,
  - Previously well, no family history
  - LFTs: **ALT 1600**, GGT 160; ALP 95; bilirubin 122
- New partner Chinese tertiary student who has strong family history of liver cancer

What next?

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- **Anti-HAV IgM neg**
- **Anti-HCV neg**
- **HBsAg neg; anti-HBs neg**

What next?

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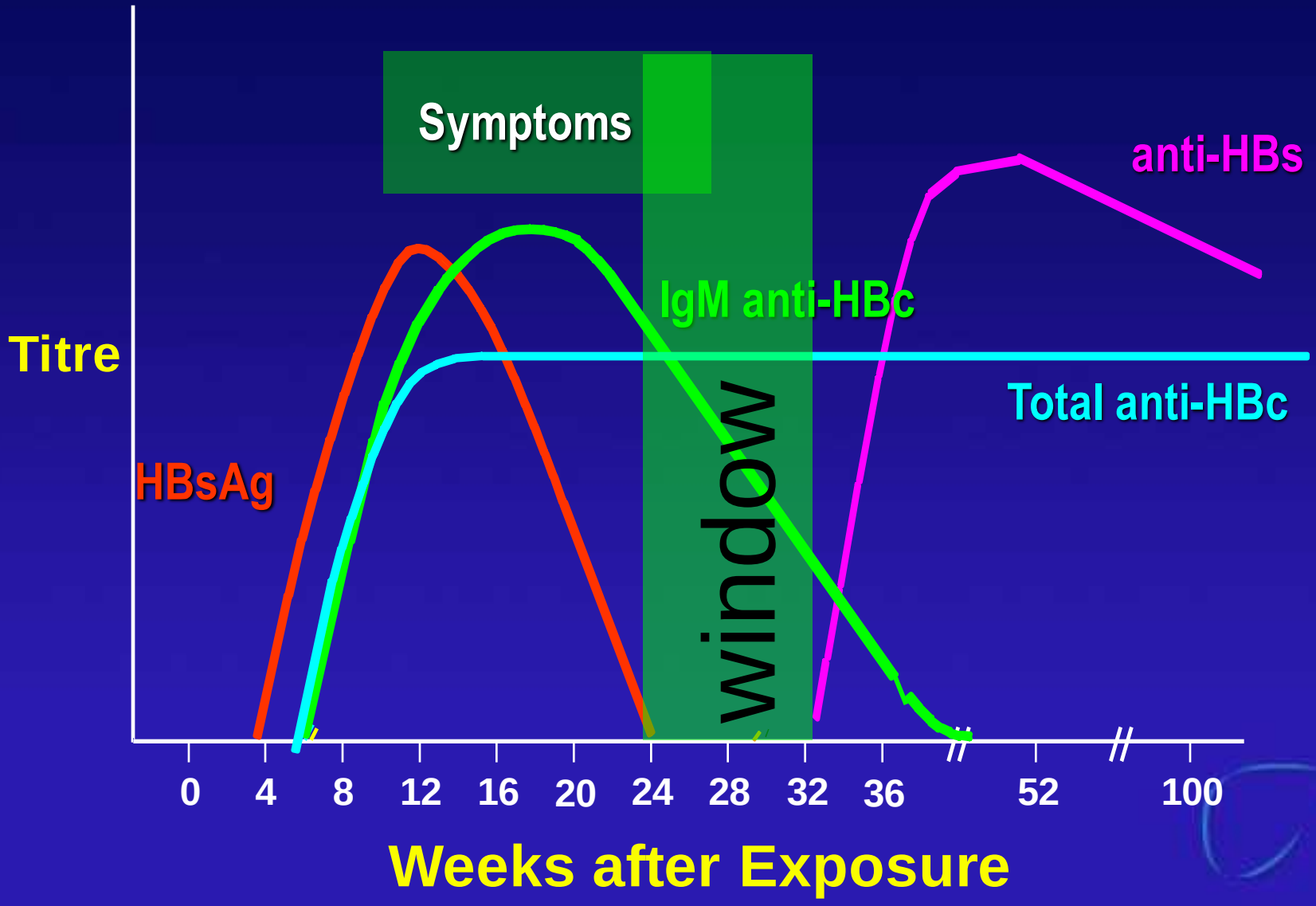
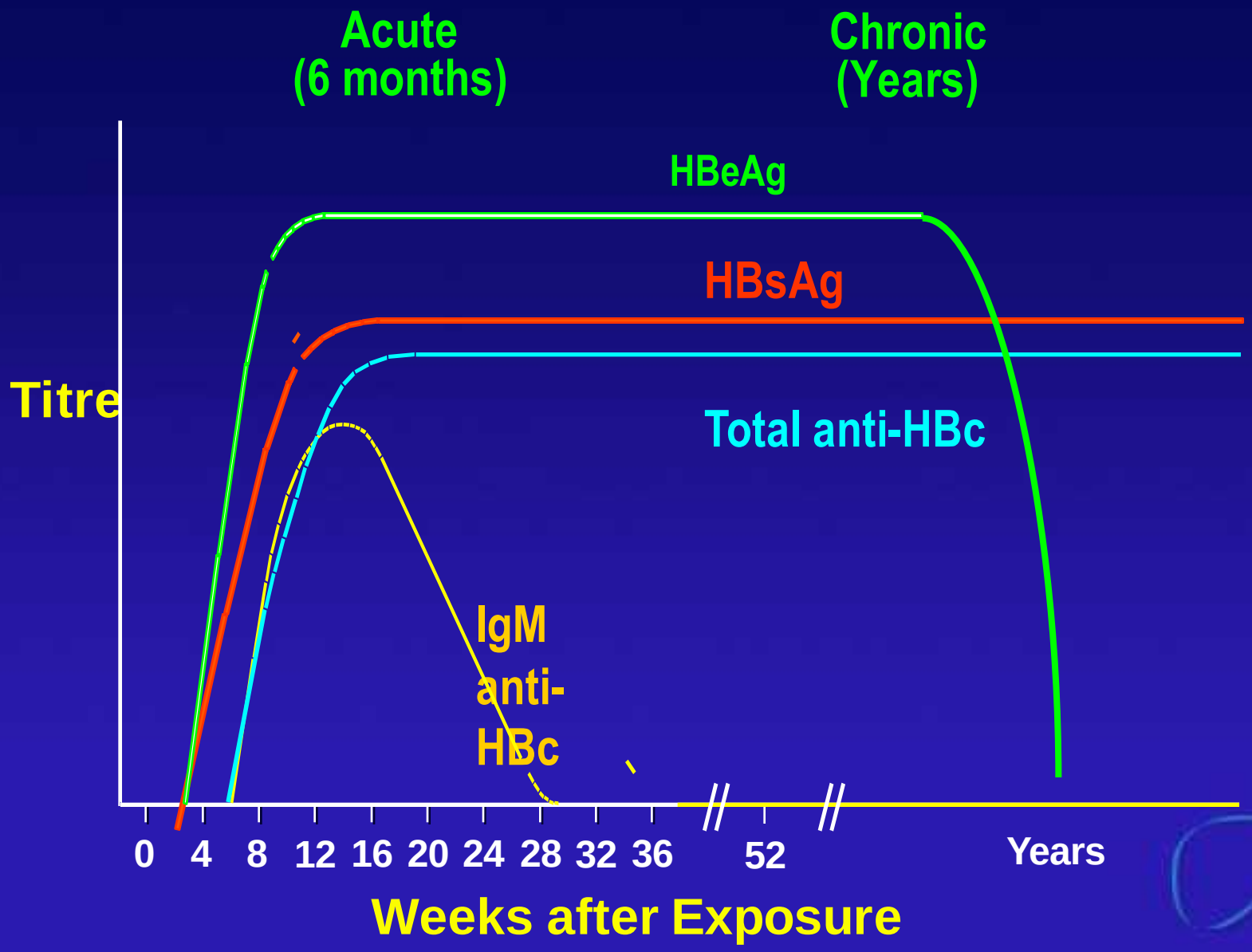
- **Anti-HAV IgM neg**
- **Anti-HCV neg**
- **HBsAg neg; anti-HBs neg**
- **Anti-HBcore IgM ++**

What next?

Diagnosis of Acute Hepatitis B



Diagnosis of Chronic Hepatitis B

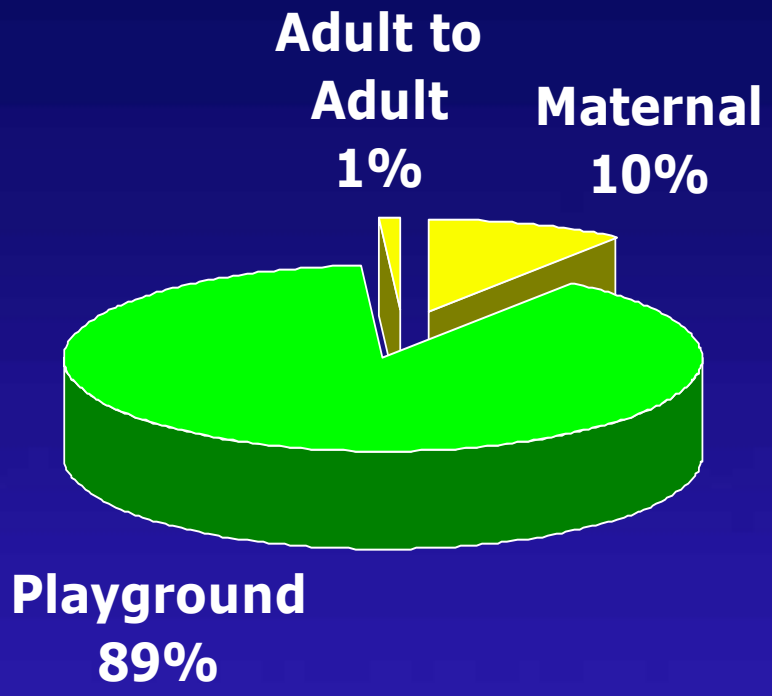


	ACUTE HBV		
	early	window	late
HB_sAg	+	±	–
anti-HBs	–	–	±
HB_eAg		–	±
anti-HBe	–	–	±
anti-HB_cIgM	+ +	+ +	+ +
anti-HB_cIgG	–	–	+
Serum ALT	>5x ULN		
HBV DNA	+	+/-	+/-

	ACUTE HBV			CHRONIC HBV	
	early	window	late	eAg+	eAg -
HB_sAg	+	±	–	+	+
anti-HBs	–	–	±	–	–
HB_eAg		–	±	+	
anti-HBe	–	–	±	–	+
anti-HB_cIgM	+ +	+ +	+ +	–	–
anti-HB_cIgG	–	–	+	+	+
Serum ALT		>5x ULN		>ULN	
HBV DNA	+	+/-	+/-	+ +	+ +

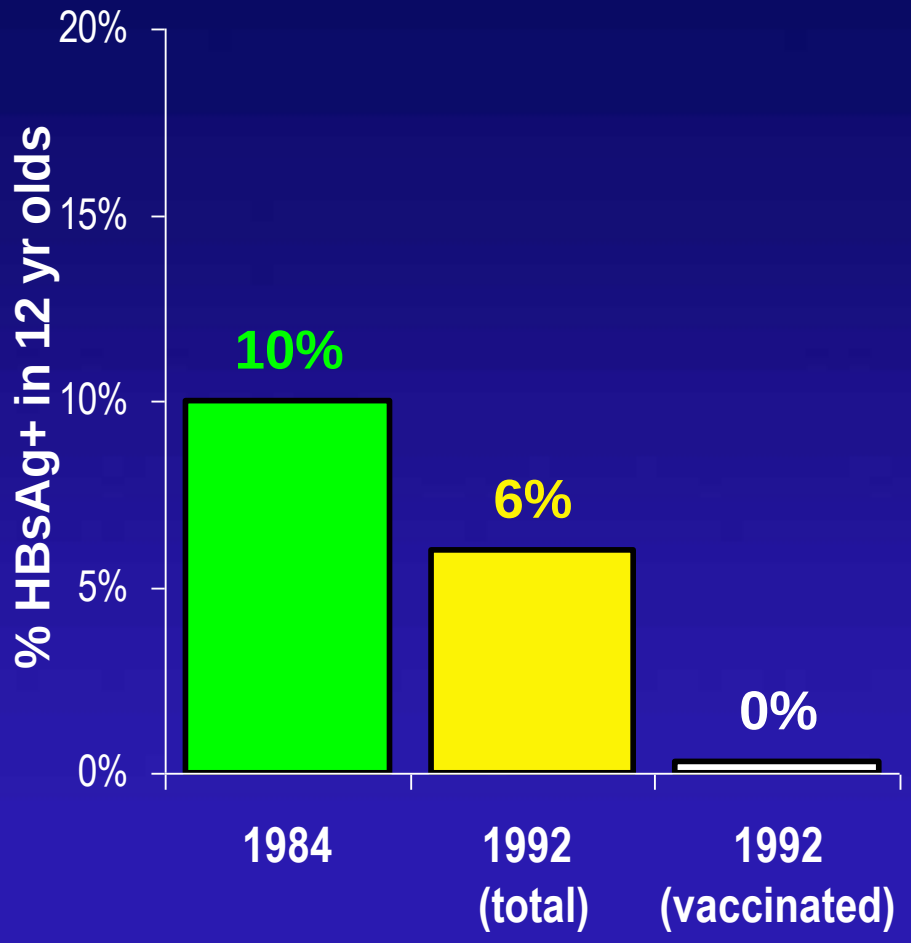
	ACUTE HBV			CHRONIC HBV		IMMUNE	
	early	window	late	eAg+	eAg -	past HBV	vaccine
HB_sAg	+	±	–	+	+	–	–
anti-HBs	–	–	±	–	–	+/-	+/-
HB_eAg		–	±	+		–	–
anti-HBe	–	–	±	–	+	+	–
anti-HB_cIgM	+ +	+ +	+ +	–	–	–	–
anti-HB_cIgG	–	–	+	+	+	+	–
Serum ALT	>5x ULN			>ULN		< ULN	
HBV DNA	+	+/-	+/-	+ +	+ +	–	–

Route of acquisition of Chronic HBV infection in NZ



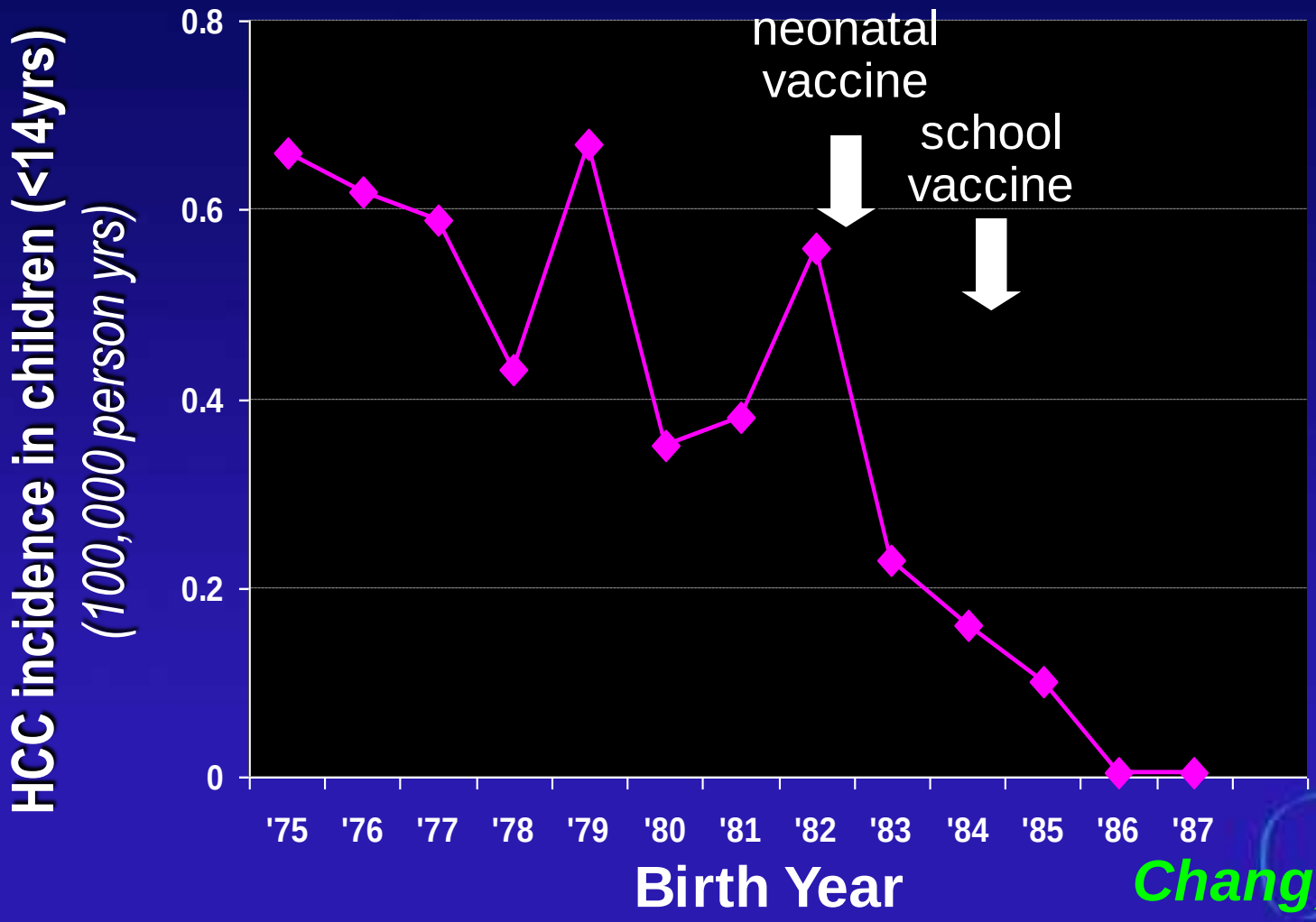
- Vaccine available, cheap, >99% effective

Control of HBV in New Zealand Neonatal Vaccination Program (1987)



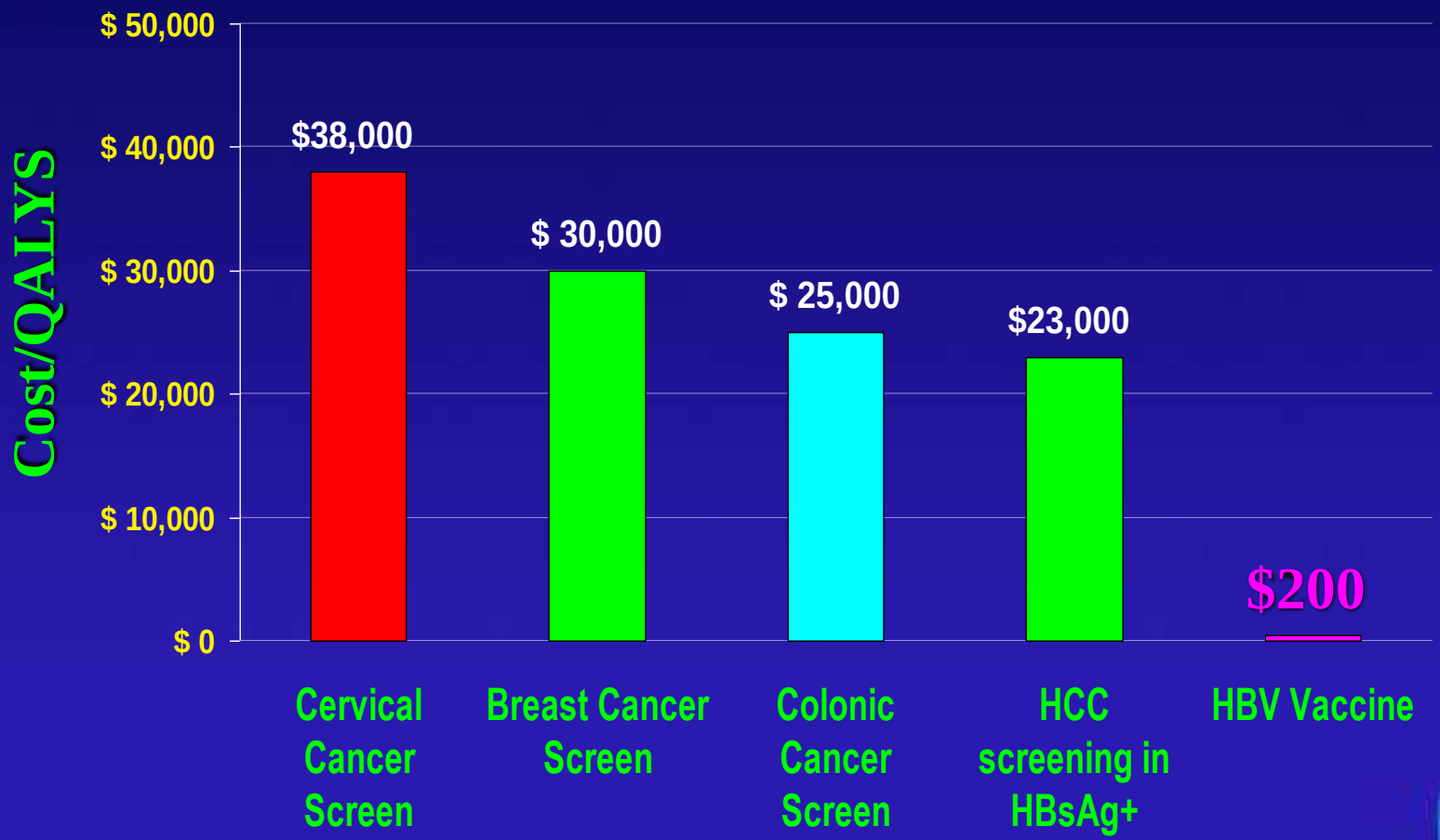
Lucas et al. *NZ Med J* 1994; 107:266-8

Prevention of HBV-related Hepatoma
Vaccination in Taiwan



Chang,1997

HCC Surveillance in Chronic HBV Infection
Cost-Effectiveness Comparison

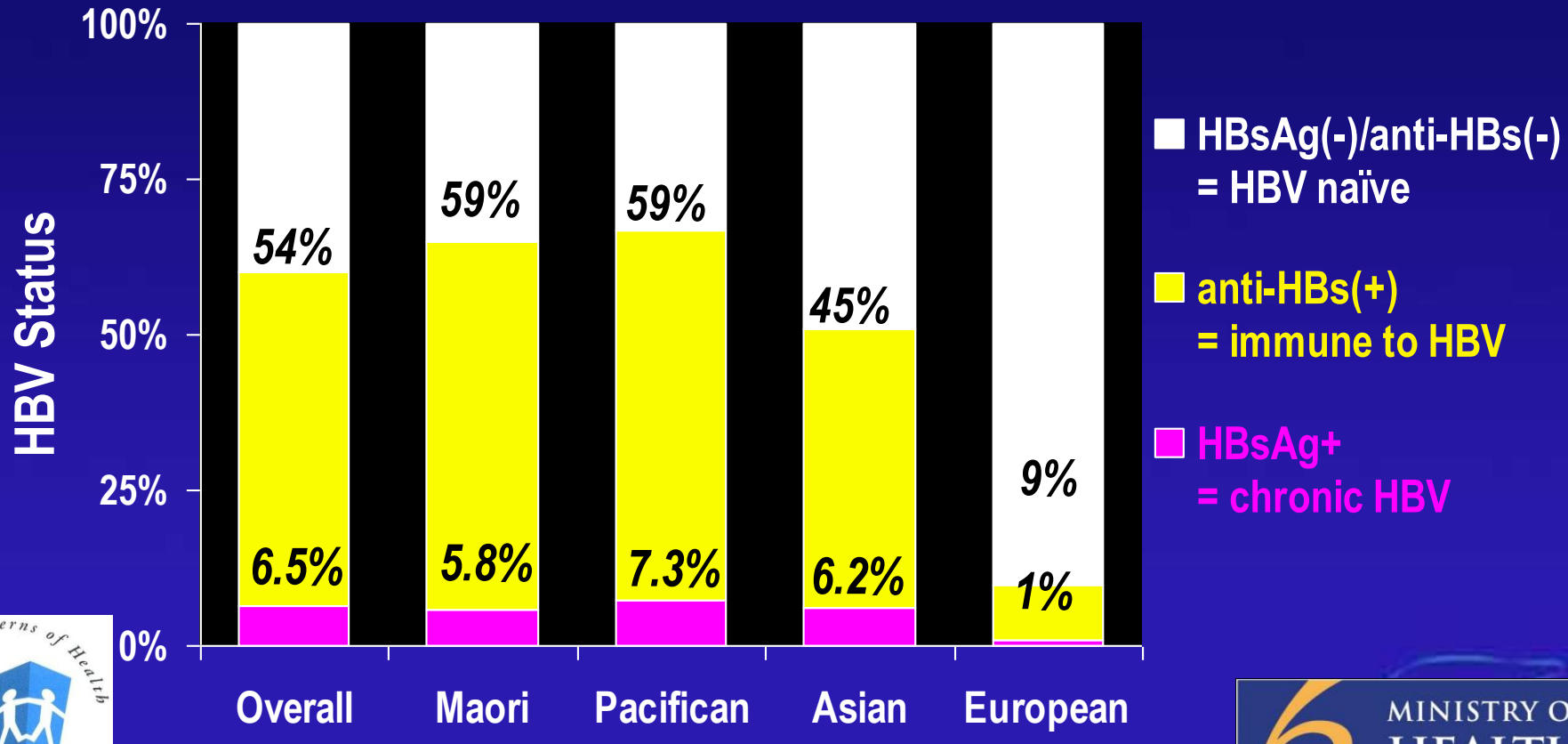


National HBV Screening Programme

Target Maori, Pacific and Asians >15 yrs

- 177,292 screened July 1999 - July 2002

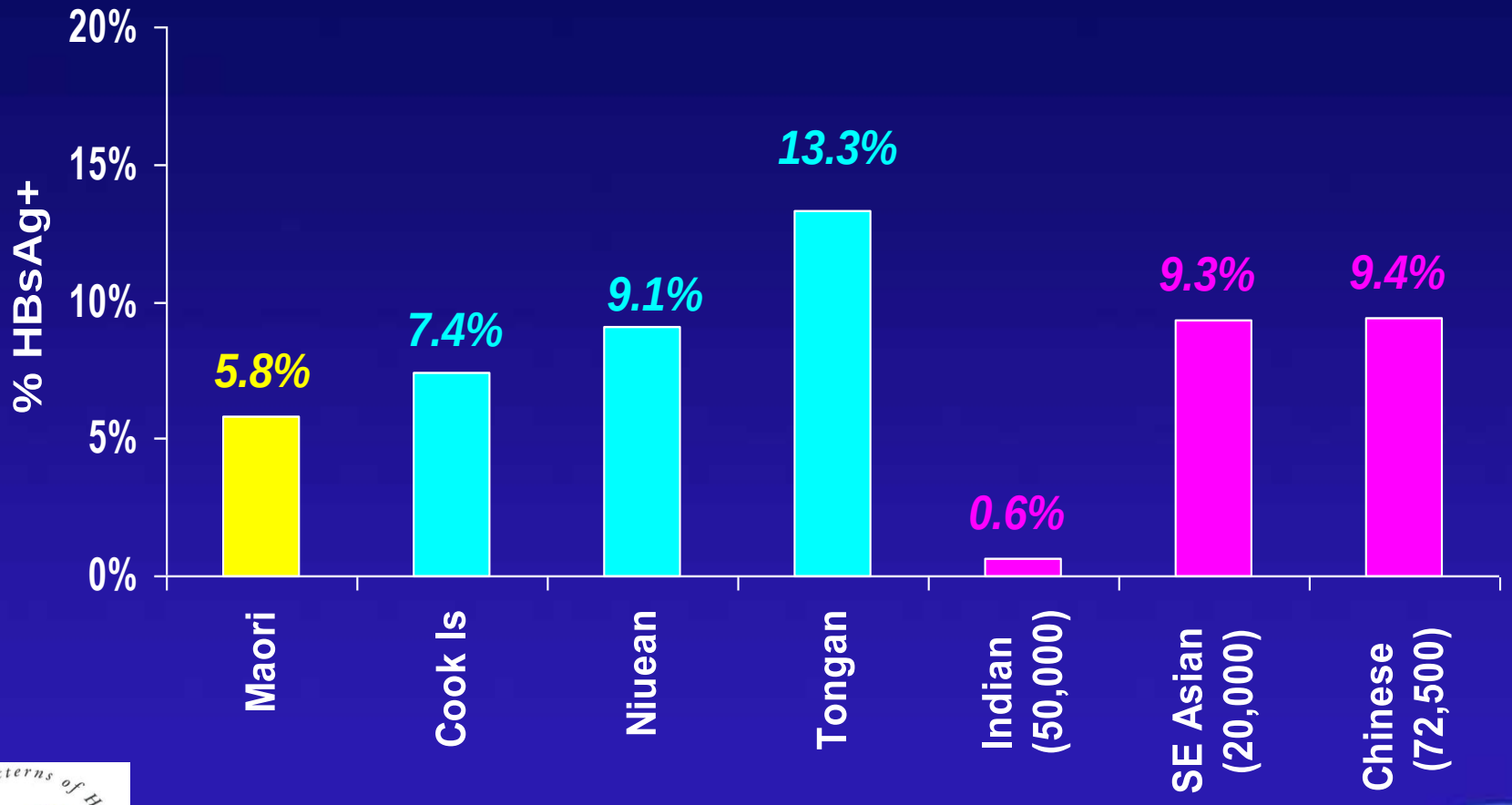
⇨ 11,300 HBsAg+ identified



Tracing Patterns of Health
THE HEPATITIS FOUNDATION

MINISTRY OF HEALTH
MANATŪ HAUORA

National HBV Screening Programme
Prevalence according to Ethnicity



Tracing Patterns of Health
THE HEPATITIS FOUNDATION

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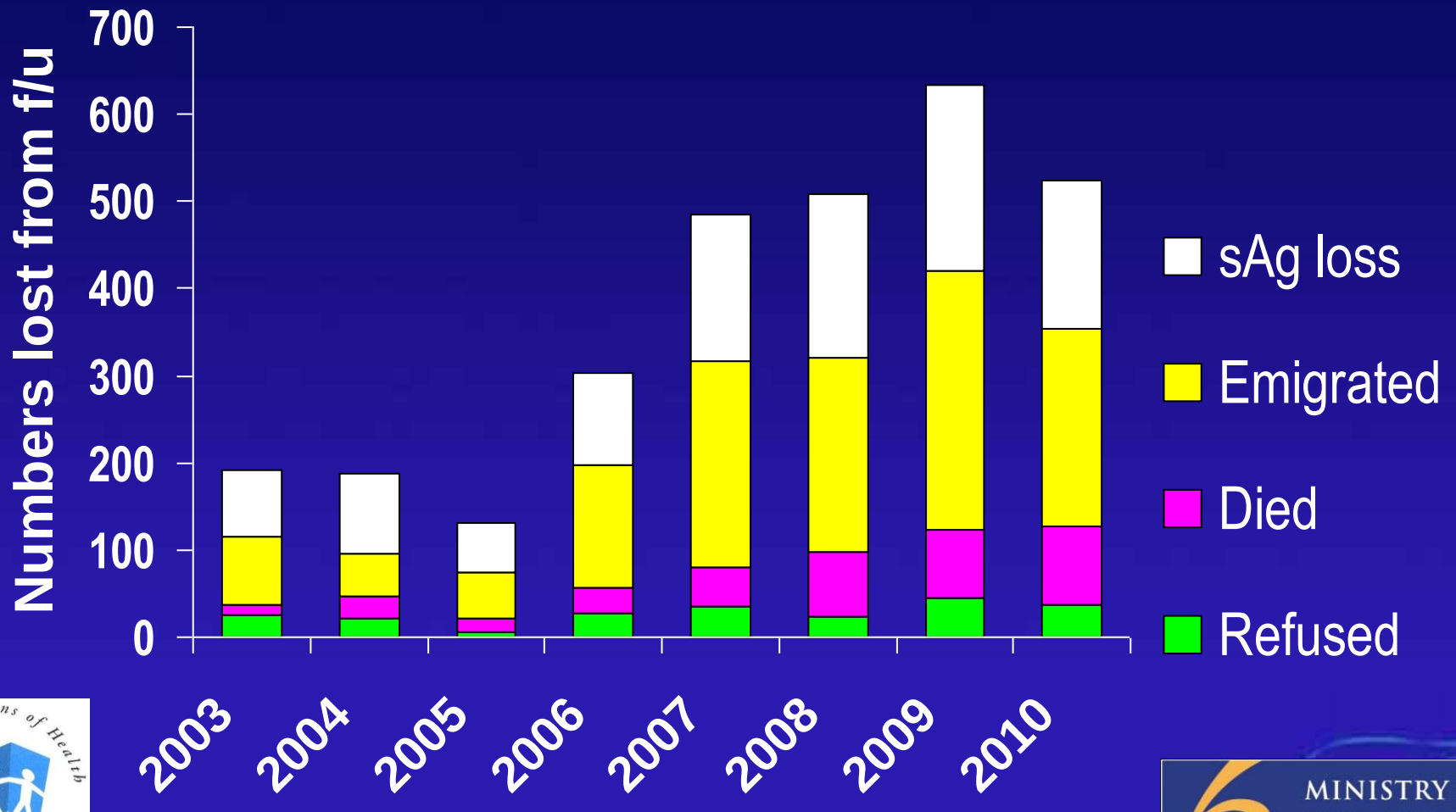
National HBV Screening Programme

- 2000-02: MoH-funded screening programme
  - »Enrolled 11,300 HBsAg+
- Since 2002: MoH surveillance programme
  - »Lost 3100 from original cohort
  - »Gained 4100 from opportunistic screening
  - »Currently 12,234 enrolled

Tracing Patterns of Health
THE HEPATITIS FOUNDATION

MINISTRY OF HEALTH
MANATŪ HAUORA

National HBV Screening Programme
Lost from Surveillance Programme



Tracing Patterns of Health
THEHEPATITISFOUNDATION

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National HBV Screening Programme
What is the future?

- Estimated 100,000 New Zealnders have HBV
- Only 12,000 in the Surveillance Programme
- Need to increase screening and follow-up
  - ➡Target Maori, Pacific Islanders and Asians

1. GPs ➡opportunistic screening

2. Reopen National Screening Program

➡Demonstrate need

➡Demonstrate benefits of screening

Tracing Patterns of Health
THEHEPATITISFOUNDATION

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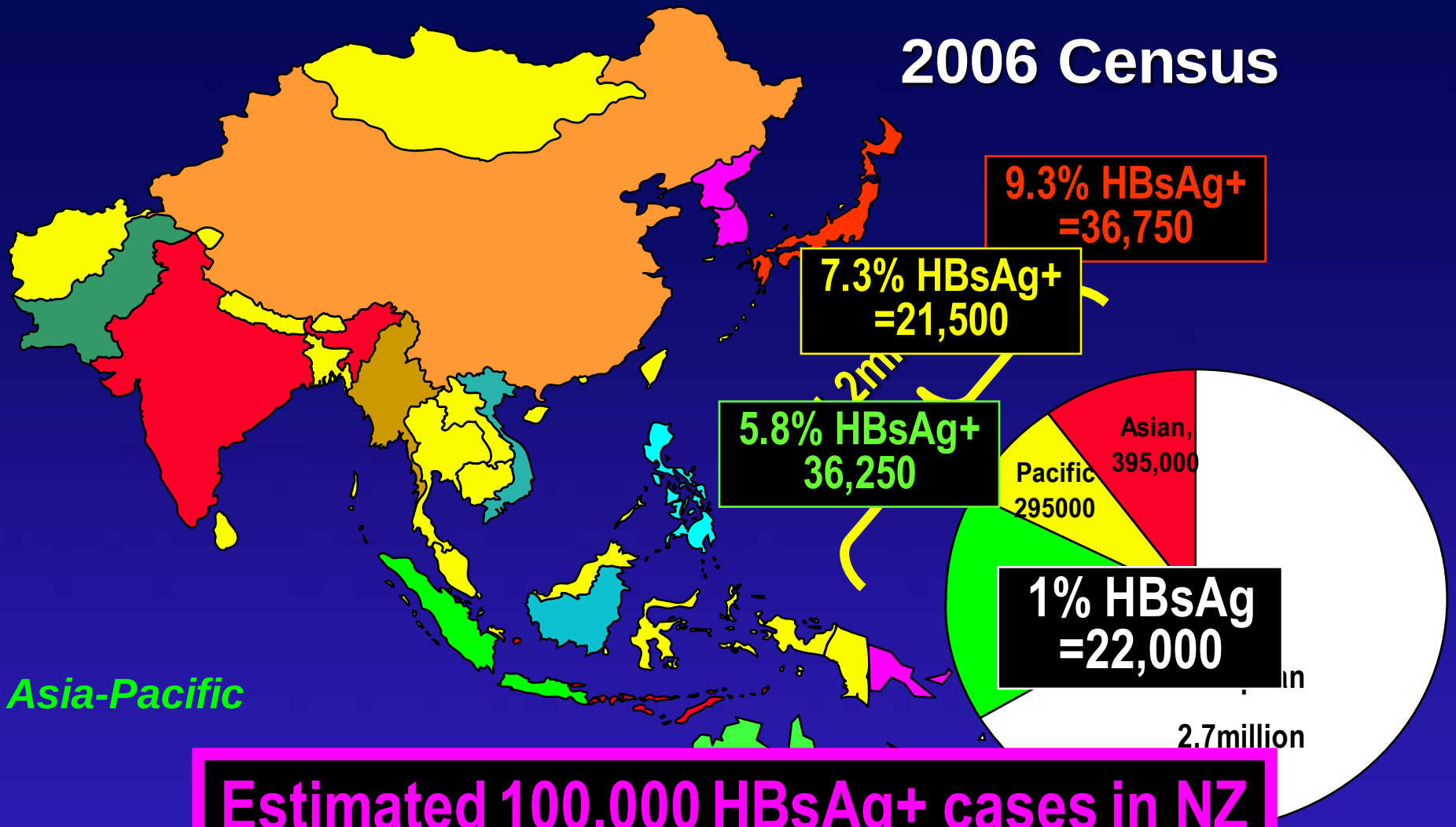
Demonstrate Need



Estimated 100,000 HBsAg+ cases in NZ

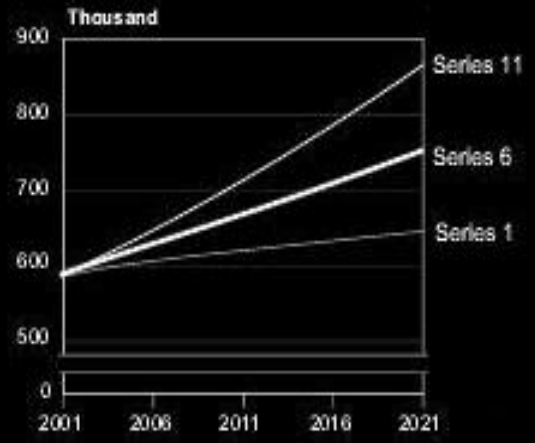
➡>60,000 cases NOT YET DETECTED

*(assumed **NO** childhood infections since 1987)*

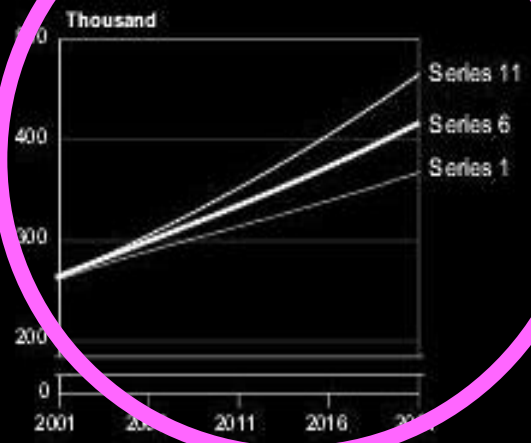
The HBV population is NOT declining

Projected Ethnic Populations 2001-'21

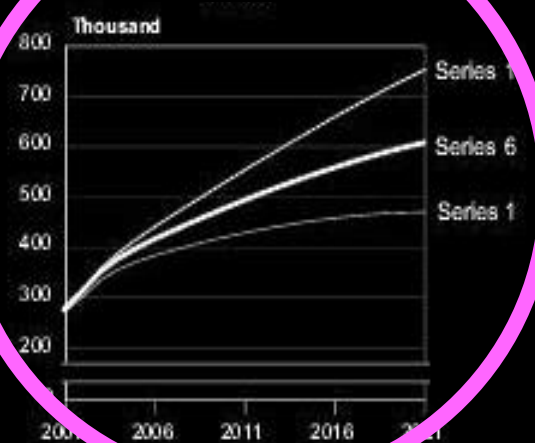
(i) Maori



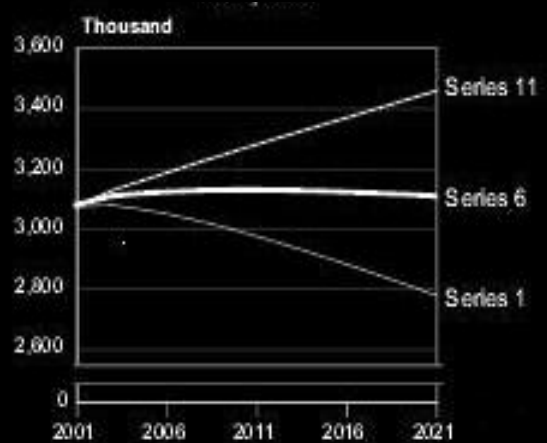
(ii) Pacific



(iii) Asian



(iv) European

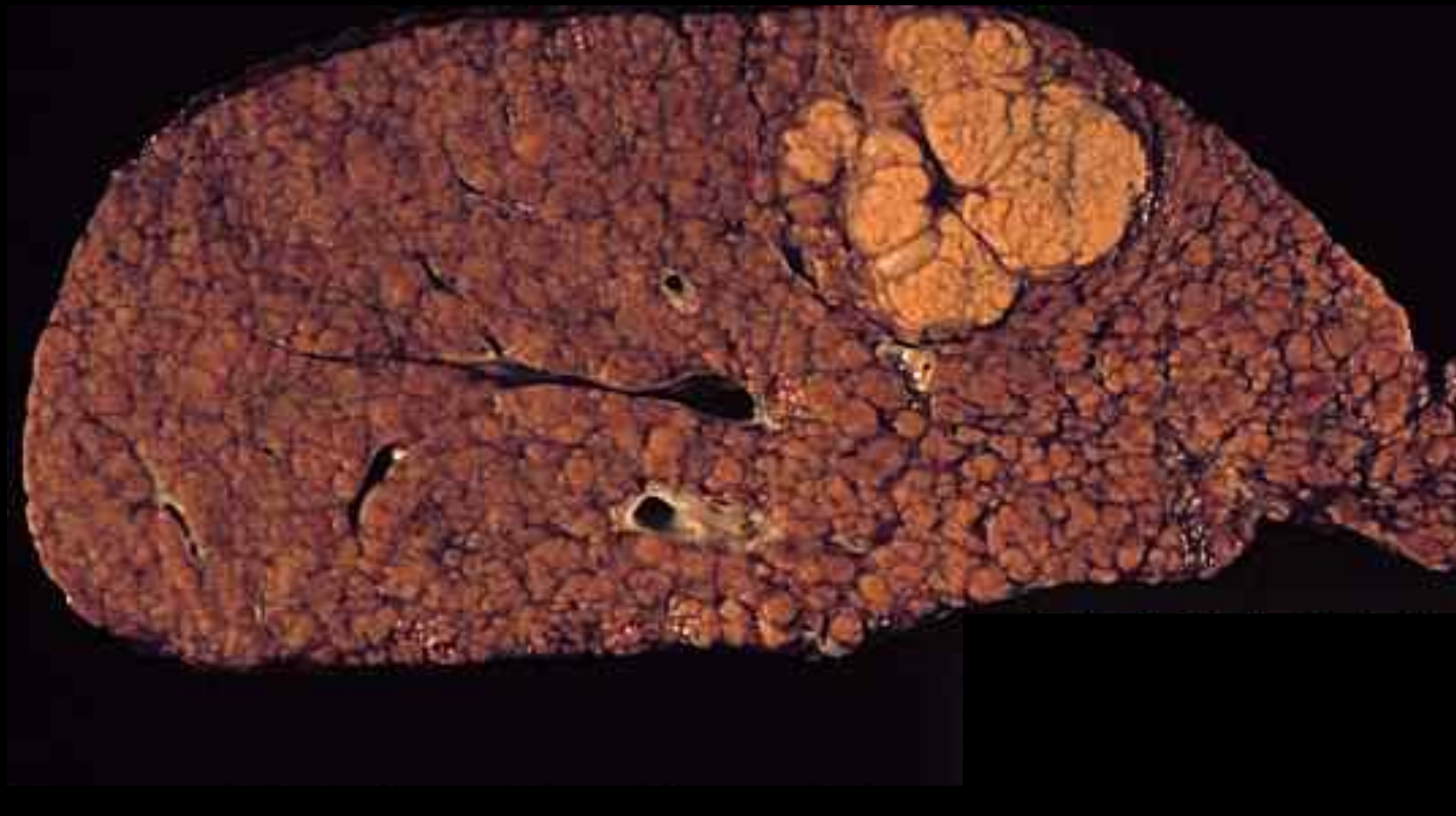


http://www.stats.govt.nz/products-and-services/Articles/pop-proj-Jun07.htm

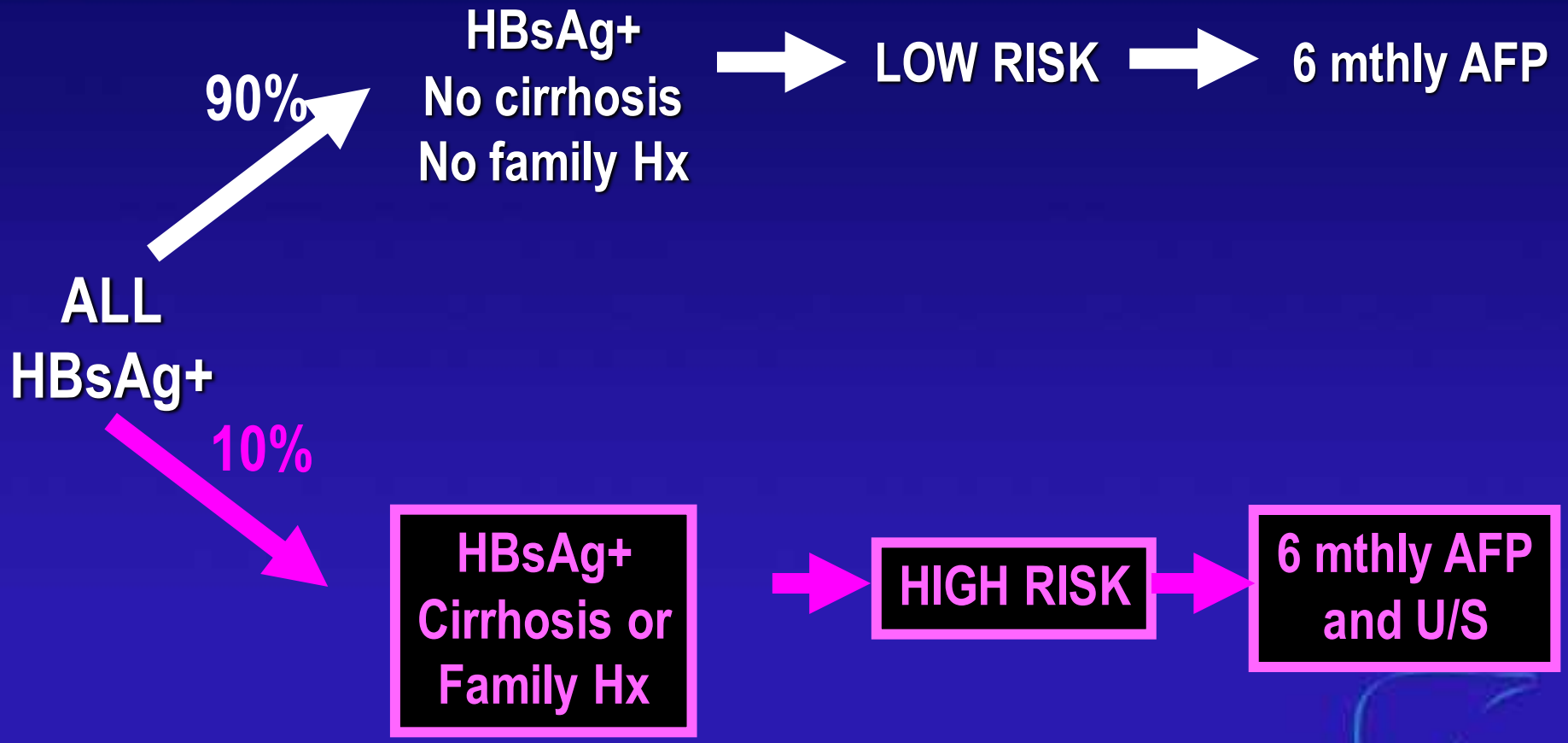
Re-open National Screening
Demonstrate Benefit

- All HBsAg+ offered 6 monthly surveillance for chronic hepatitis and liver cancer (HCC)
  - »Safe, effective surveillance tests (AFP, ALT)
  - »Effective treatments available
    - HCC ⇨ ablation/resection
    - Chronic hepatitis ⇨ antiviral therapy
  - »Do treatments improve survival?

National HBV Surveillance Improves survival



National HBV Follow-up Programme
Surveillance for Hepatoma



National HBV-HCC Surveillance Programme
Outcomes to date (2002-2010)

Patients in the NZ HBV Screening Program

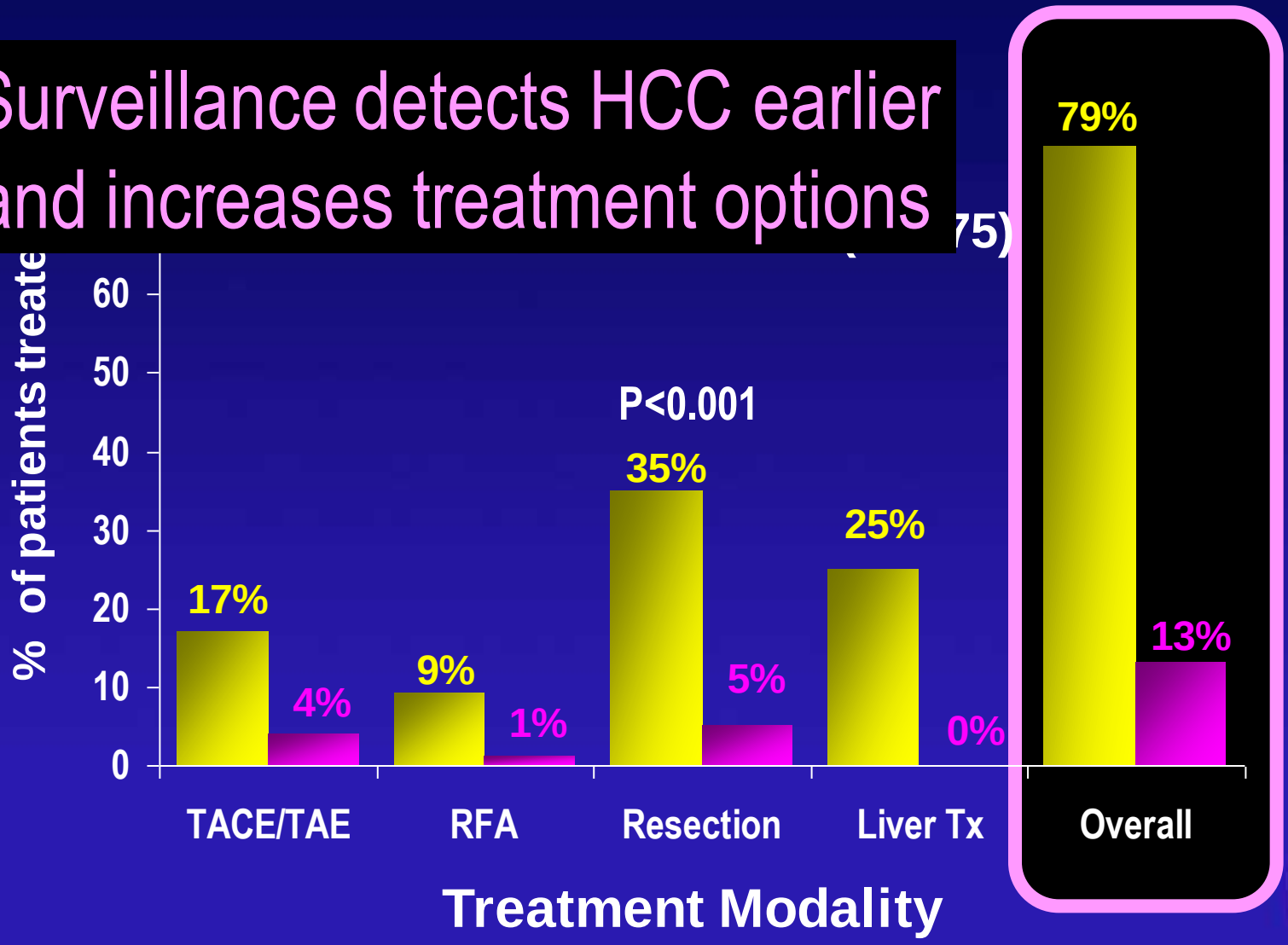
→ 190 HCCs
- Detected at screening visit
- Detected between visits

Patients NOT enrolled in HBV Screening Program

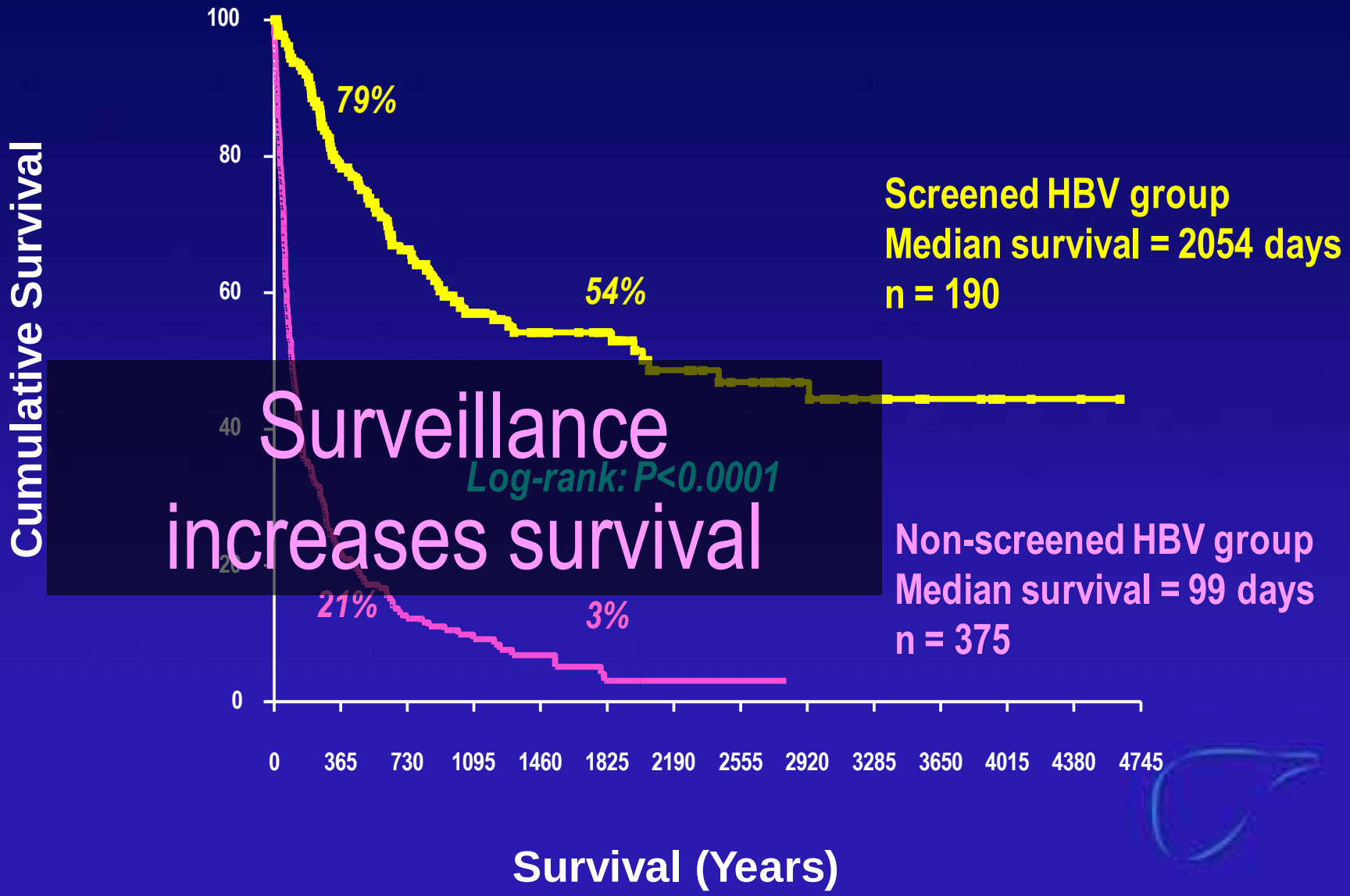
→ 375 Non-screened HCCs
- All symptomatic

Surveillance in HBV increases chance of curative treatment for HCC

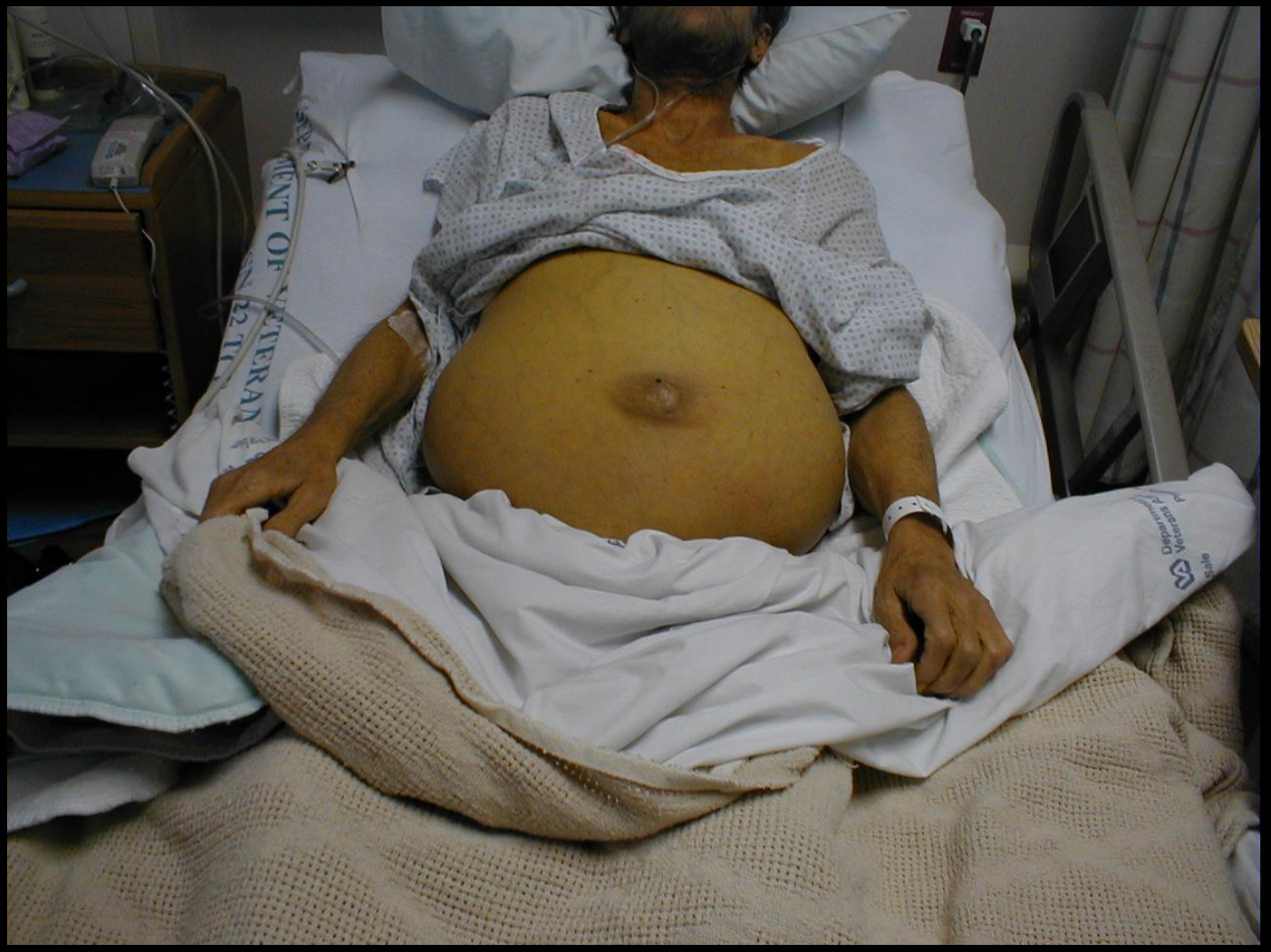
Surveillance detects HCC earlier and increases treatment options



Surveillance in HBV increases survival



National HBV Surveillance Improves survival



Goals of treatment in CHB: APASL Consensus Statement 2005

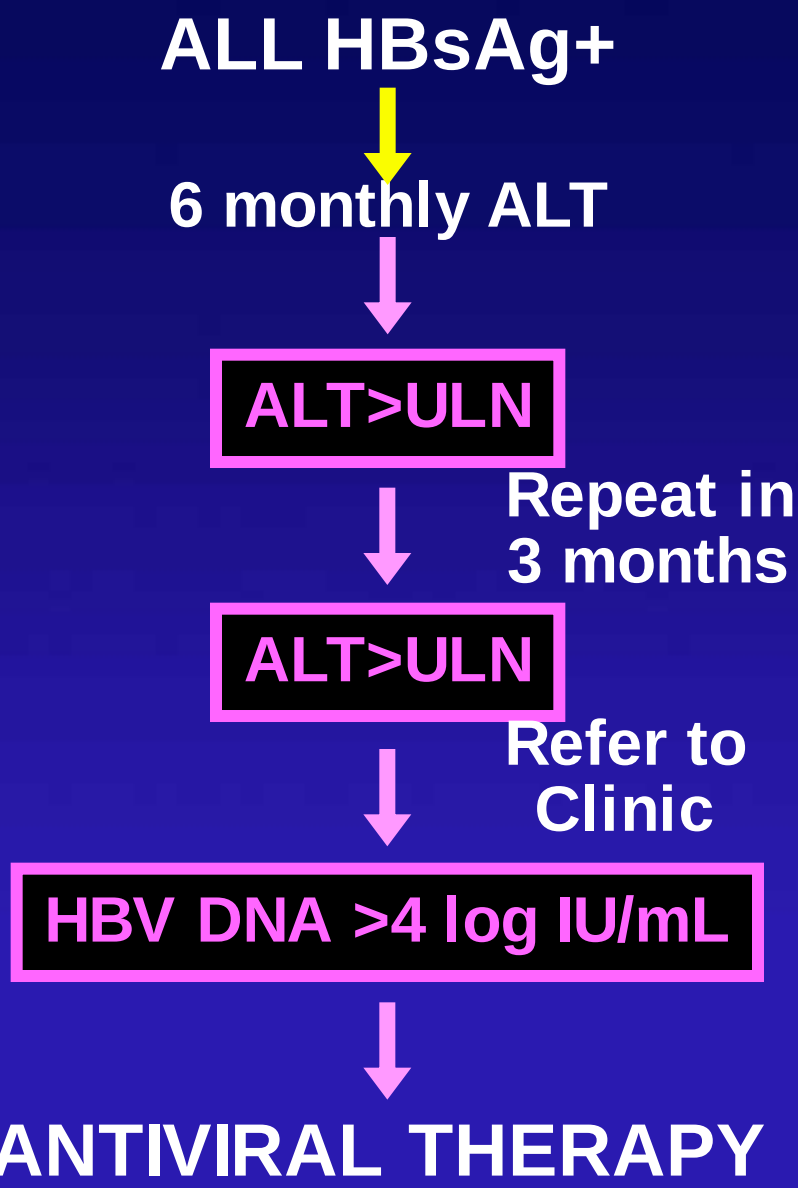
"The ultimate long-term goal is prevention of cirrhosis, decompensation and HCC, and prolong survival.

Sustained viral suppression is the key to the reduction or prevention of hepatic injury and disease progression.

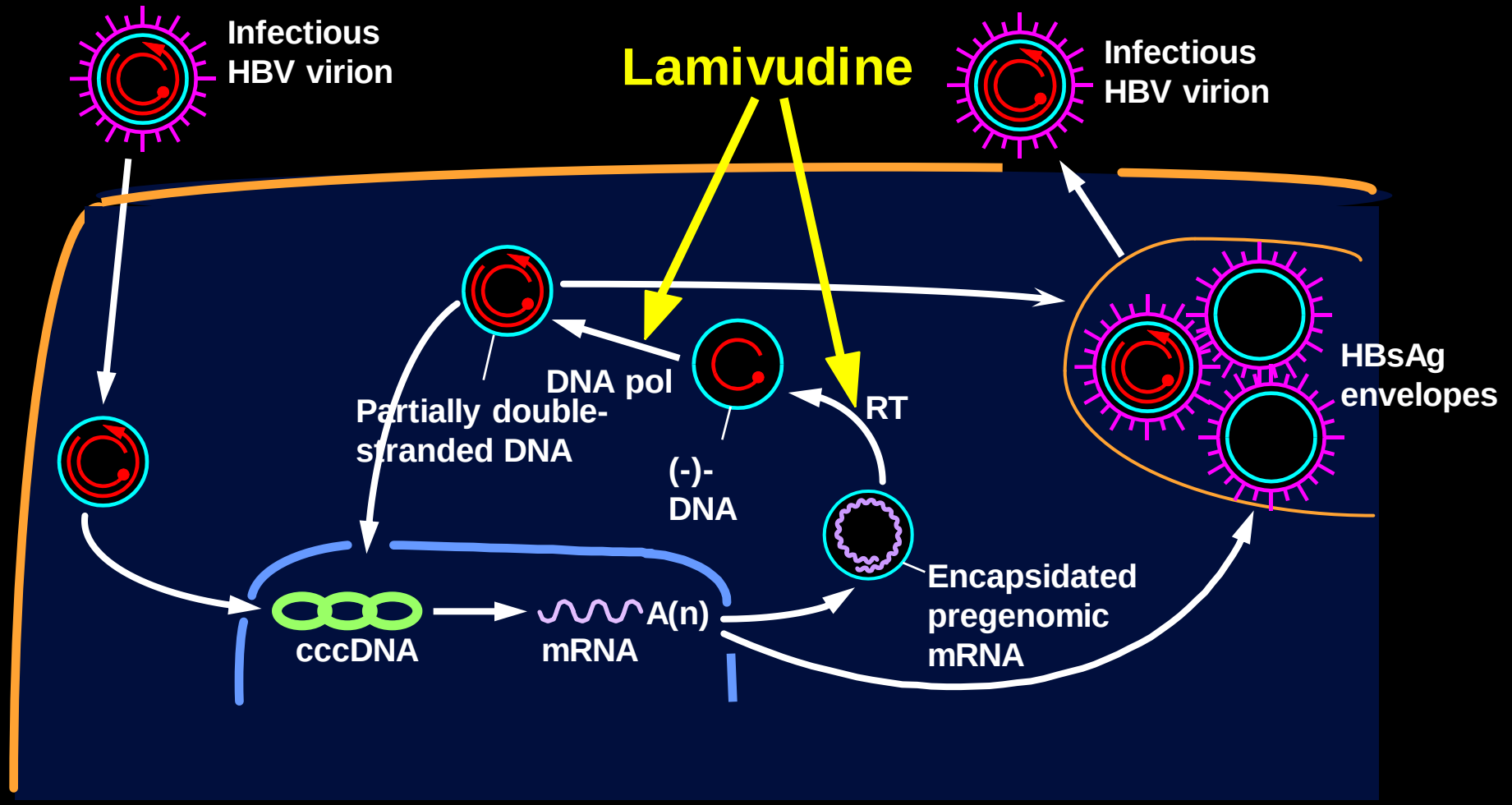
Therefore, the primary goal of treatment for chronic hepatitis B is to eliminate or permanently suppress HBV….. "

Liaw YF et al. Liver Int 2005

National HBV Follow-up Programme
Surveillance for Chronic Hepatitis



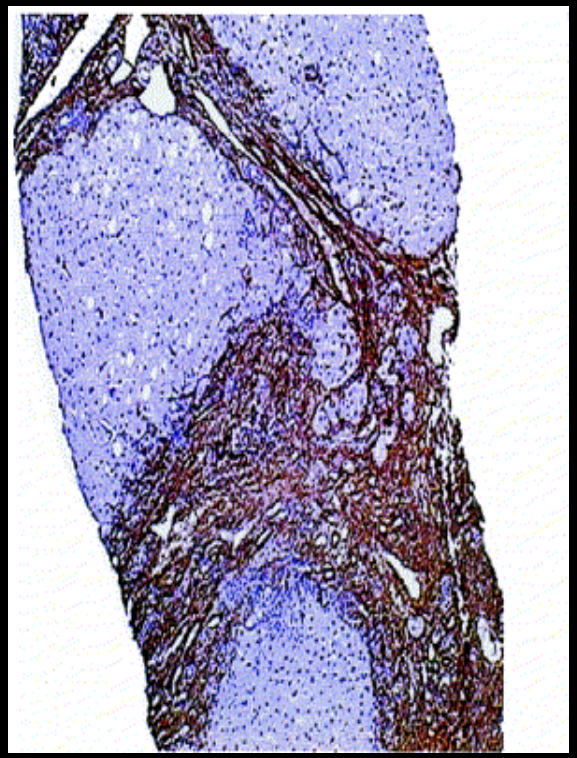
Replication Cycle of Hepatitis B Virus; Mechanism of Action of Lamivudine



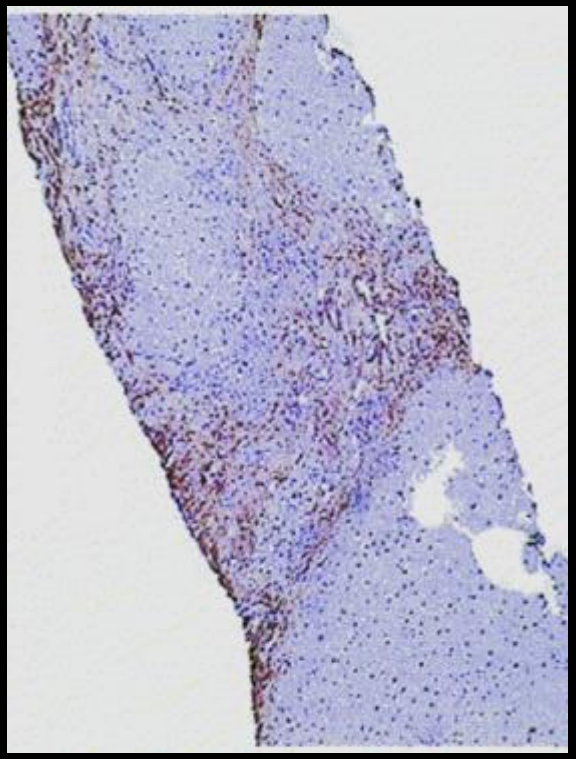
Lai *et al.*, J Med Virol 2000

Treatment in HBV prevents and reverses Cirrhosis

Pre-treatment
Cirrhosis



After 3 years Lamivudine
Mild Fibrosis

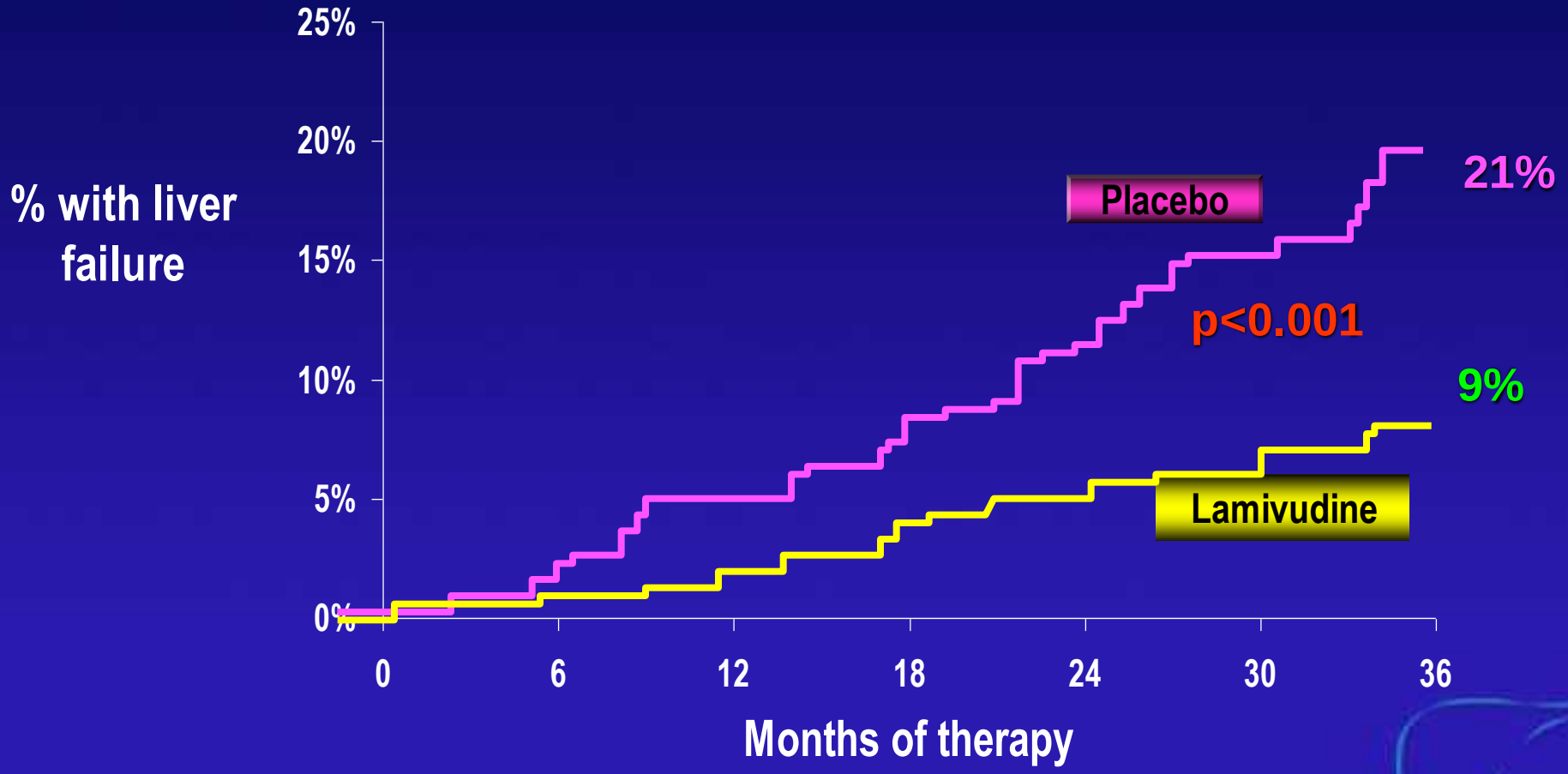


Dienstag,2003

Viral Suppression with Lamivudine may prevent Liver Failure

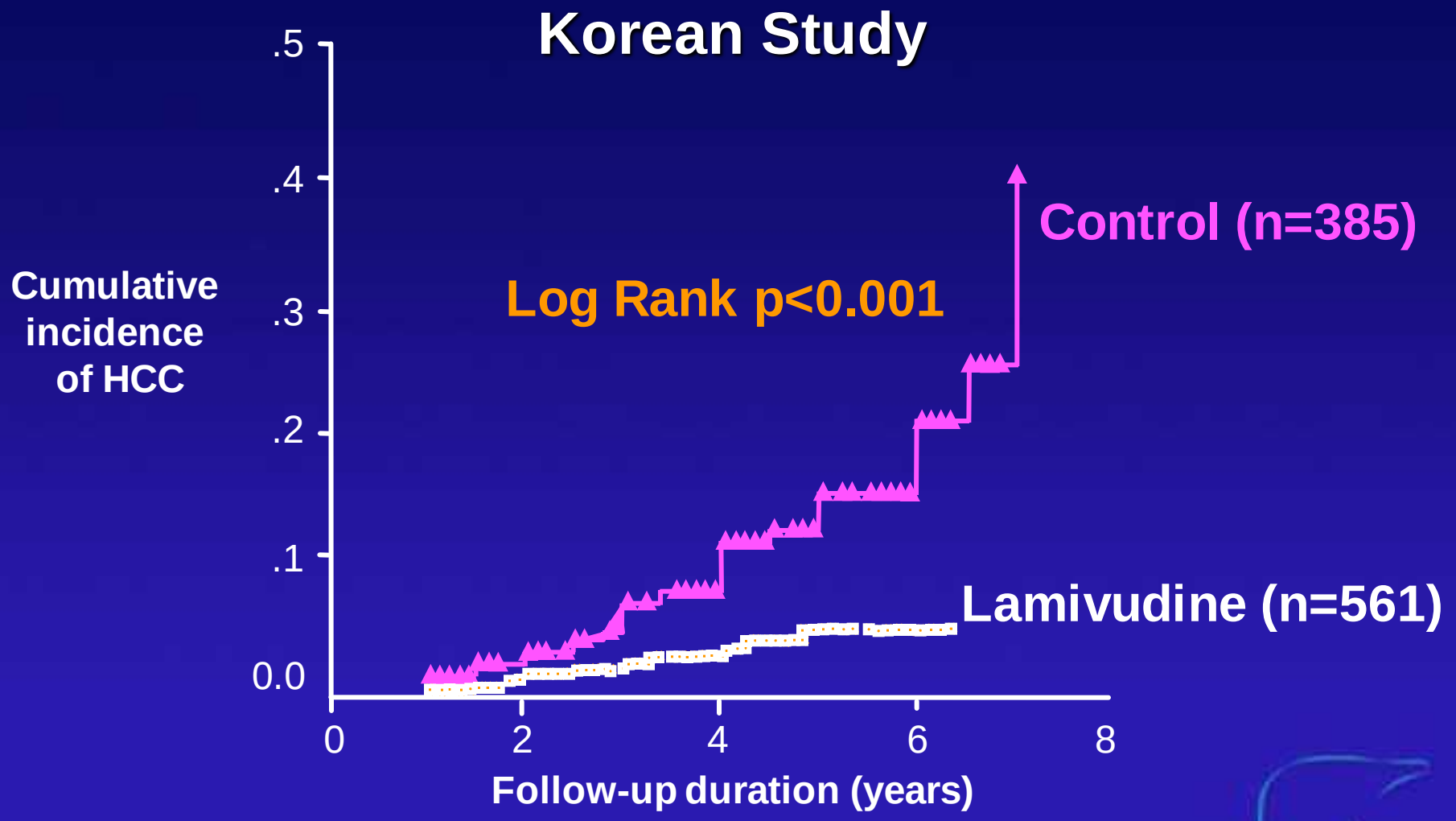
Cirrhosis Asian Lamivudine Multicenter study

RCT of 651 Pts with compensated HBV-cirrhosis



Liaw YF. *NEJM*. 2004;351:1521-1531.

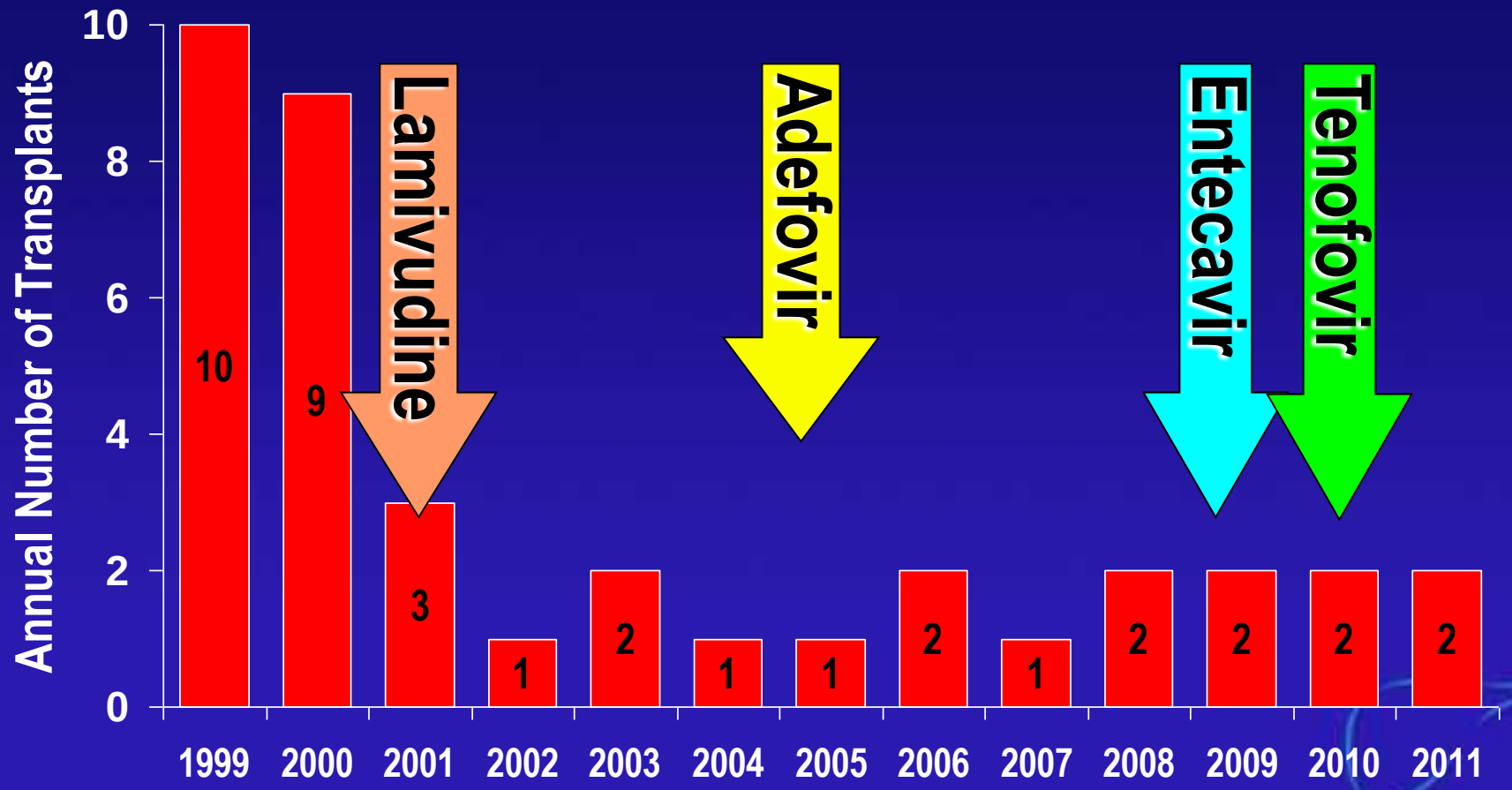
Viral Suppression with Lamivudine may prevent Hepatocellular Carcinoma



Eun JR et al. *J Hepatol* 2010; 53: 118-25

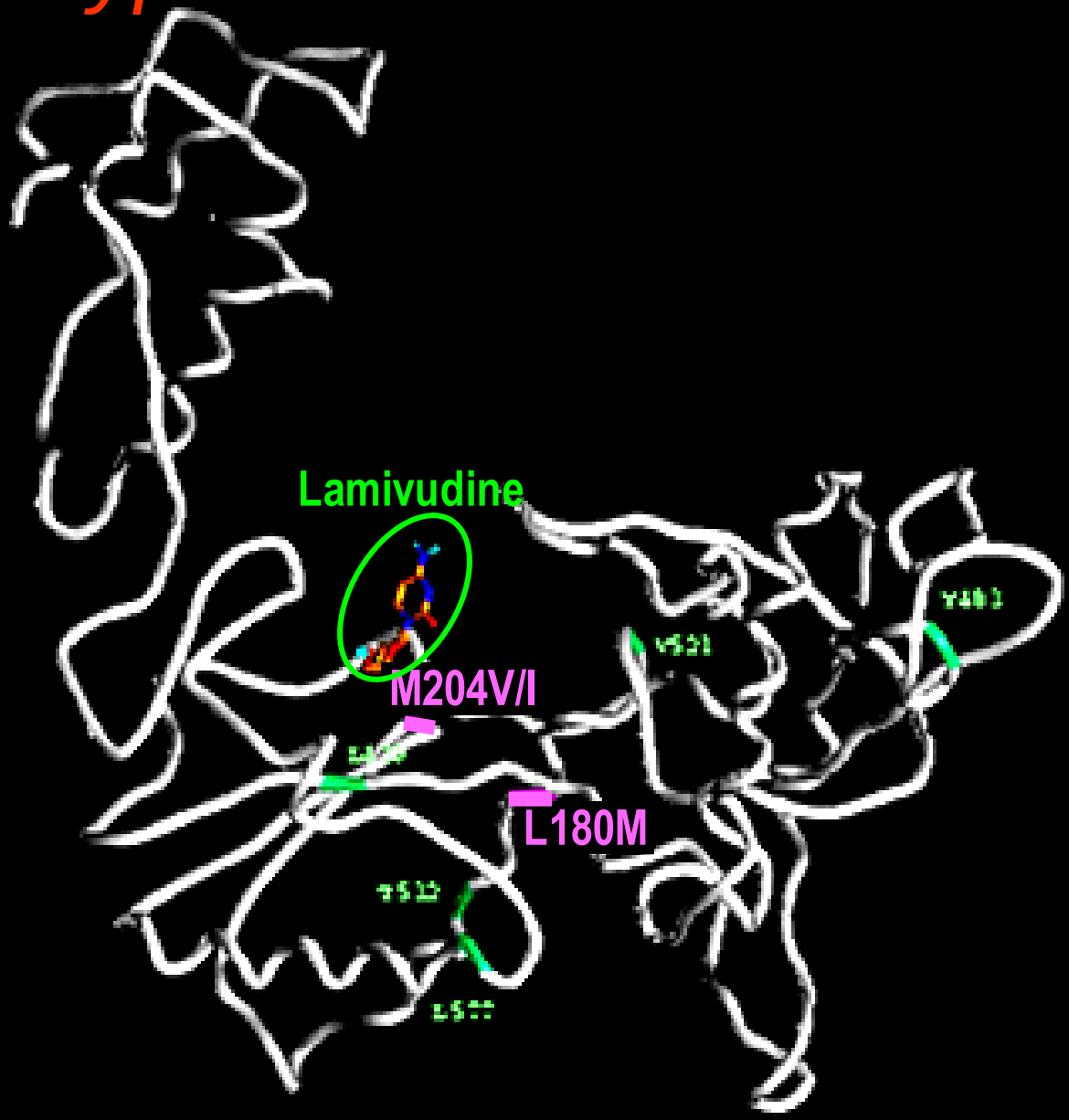
Viral Suppression with Lamivudine may prevent Liver Transplantation

Transplants for Decompensated CHB



NZLTU data 1999-2011

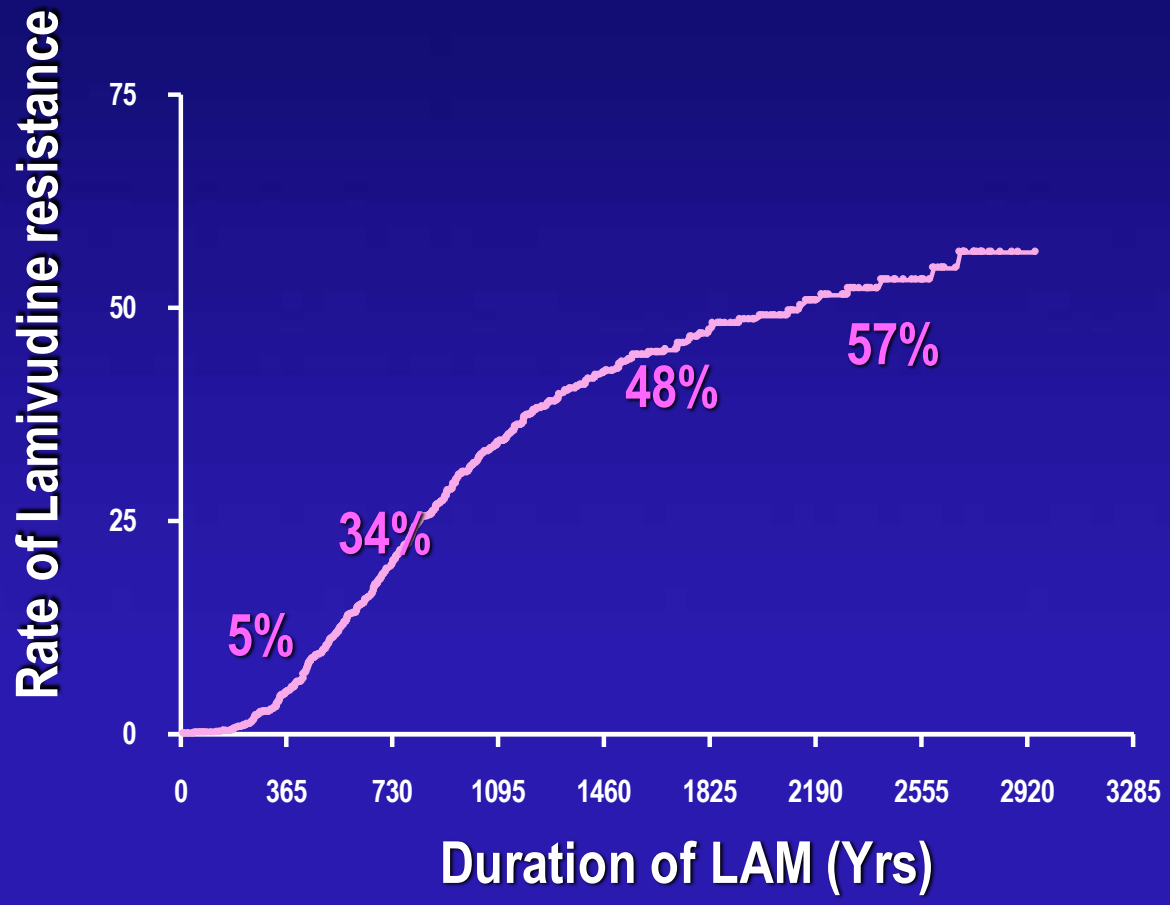
Genotypic Lamivudine Resistance



Lamivudine in NZ
Auckland HBV Clinic (1999-2009)

1254 treated with Lamiv

- **Breakthrough in 422 (↑DNA >1 log)**



Options for Lamivudine-resistant CHB

(a) L-Nucleosides

Lamivudine

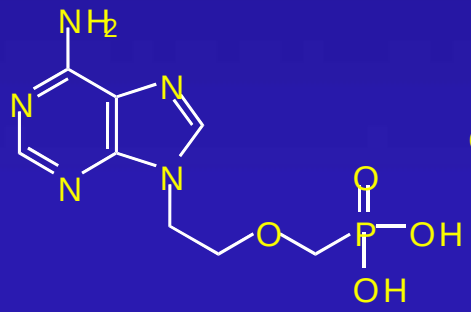
Telbivudine

Emtricitabine

(b) D-Cyclopentane

Entecavir

(c) Acyclic Phosphonate

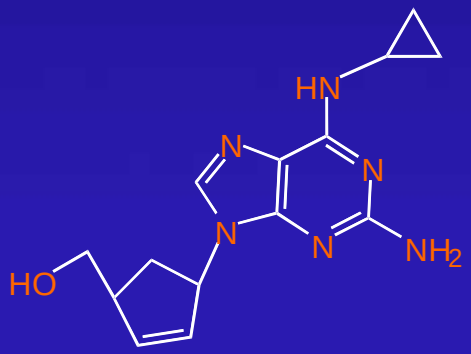


Adefovir

Tenofovir

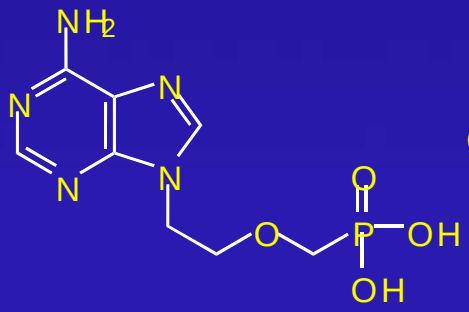
Options for Lamivudine-resistant CHB

(b) D-Cyclopentane



Entecavir

(c) Acyclic Phosphonate



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Options for Lamivudine-resistant CHB

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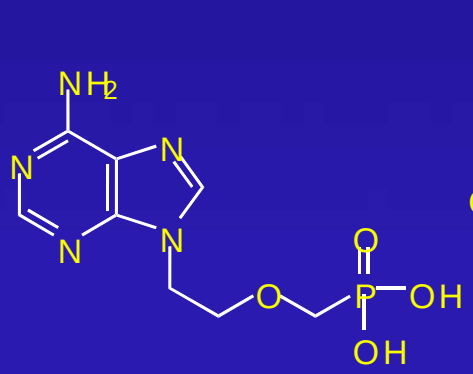

Adefovir

Tenofovir

Resistance to Nucleoside Analogues

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Management of CHB in NZ
Summary

- **>100,000 New Zealanders have chronic HBV**
  - »>10,000 New Zealanders have HBV-cirrhosis
  - »200 die each year from HCC/liver failure
- **Suppression of HBV with antiviral therapy prevents disease progression and reverses liver cirrhosis**
- **Current treatments (entecavir, tenofovir) are safe and 100% effective and fully funded for life**
- **Life-long antiviral therapy prevents disease progression and reverses liver cirrhosis**
- **Earlier diagnosis and treatment will prevent liver cancer, liver failure, transplant and death**

Management of CHB in NZ
Challenges

- < 25% all HBsAg+ patients have been recruited into regular follow-up
- <5% all active CHB receive antiviral Rx
- Most cases of liver cancer and cirrhosis present late with symptoms of advanced disease, when therapeutic options are limited and survival poor (<3 months)
- Outcomes can only be improved from earlier diagnosis and surveillance

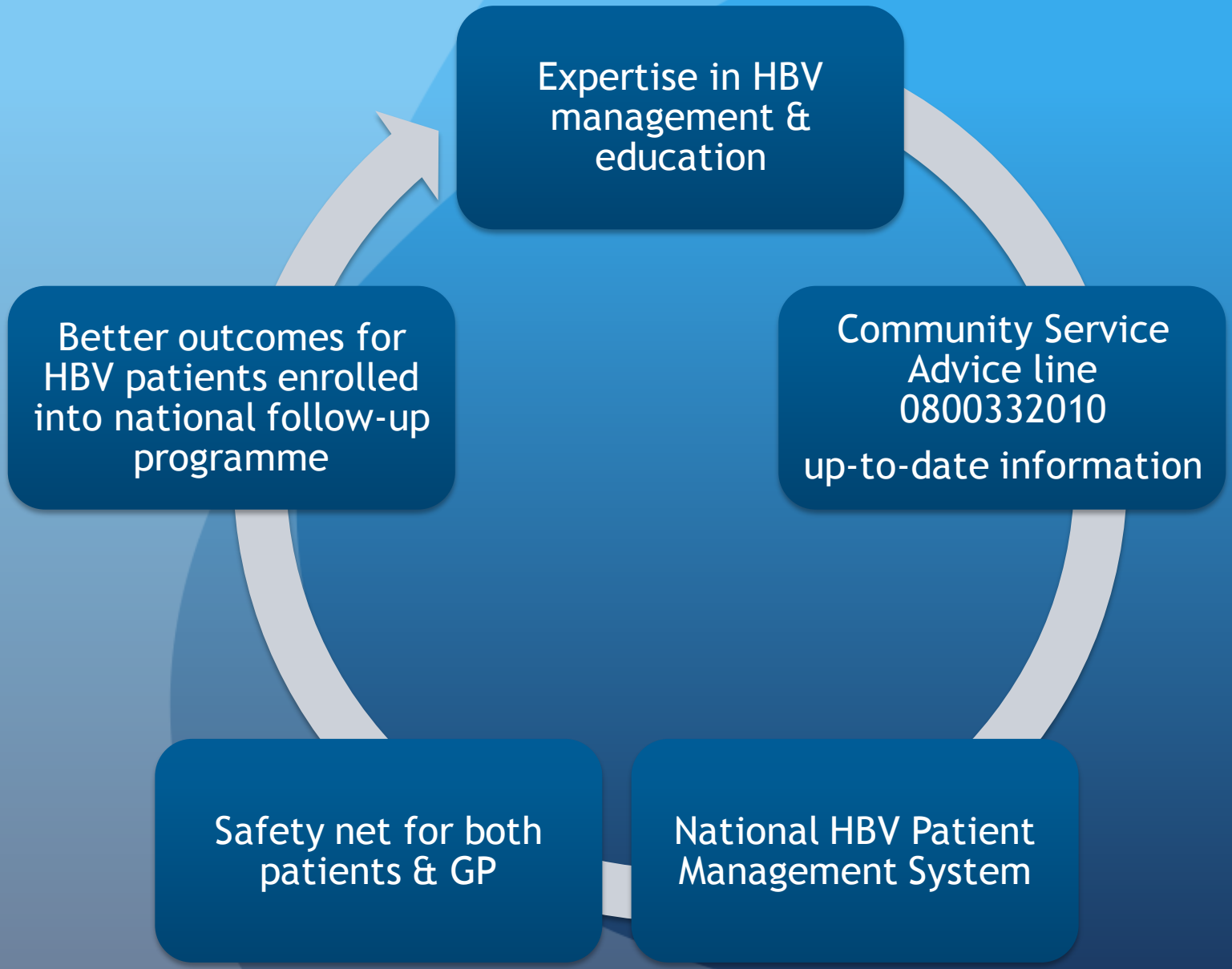
Hepatitis Foundation of New Zealand

The Story So Far?

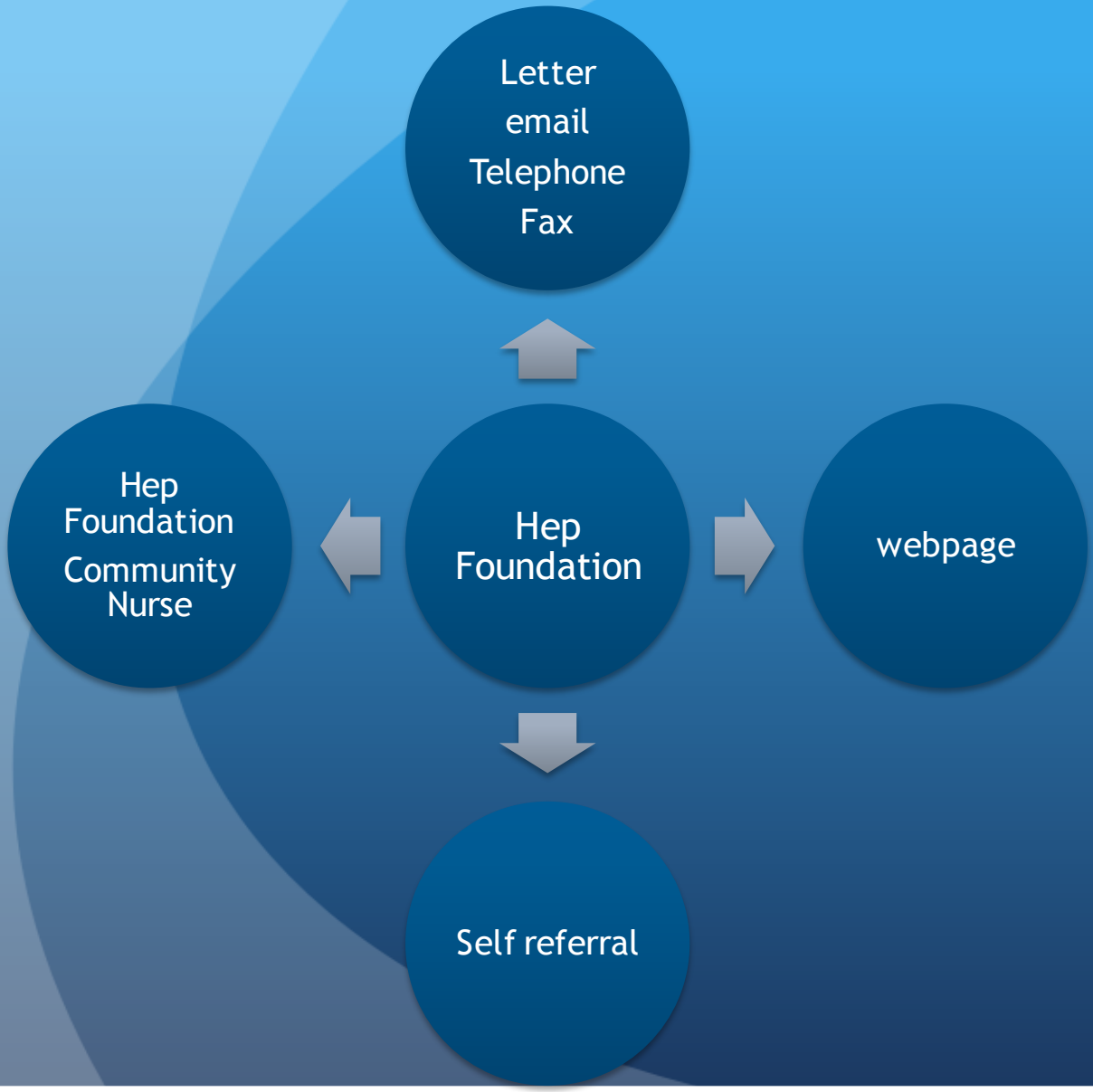
History so far

- Established 30 years ago
- Charitable Trust
- Head office in Whakatane
- Largest HBV follow-programme globally
- Employs 22 staff
- Works in partnership with the NZ Liver Unit
- Has over 12,000 clients enrolled in long-term follow-up

Why use the Hepatitis Foundation?



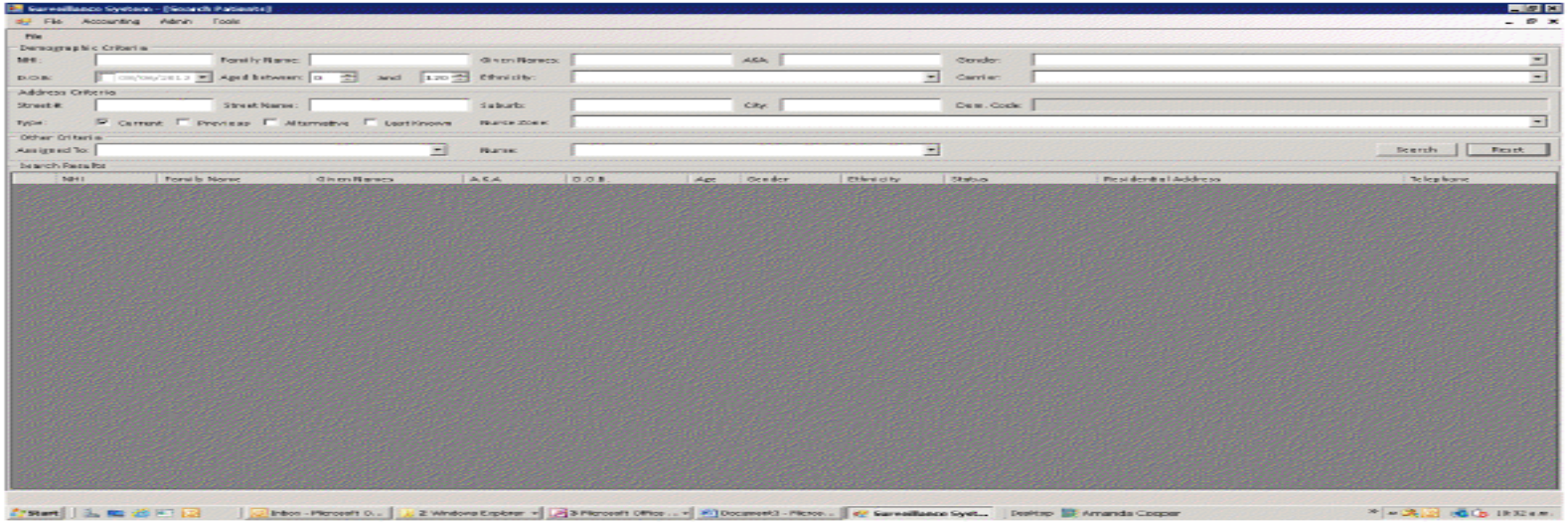
How to refer from Primary Care



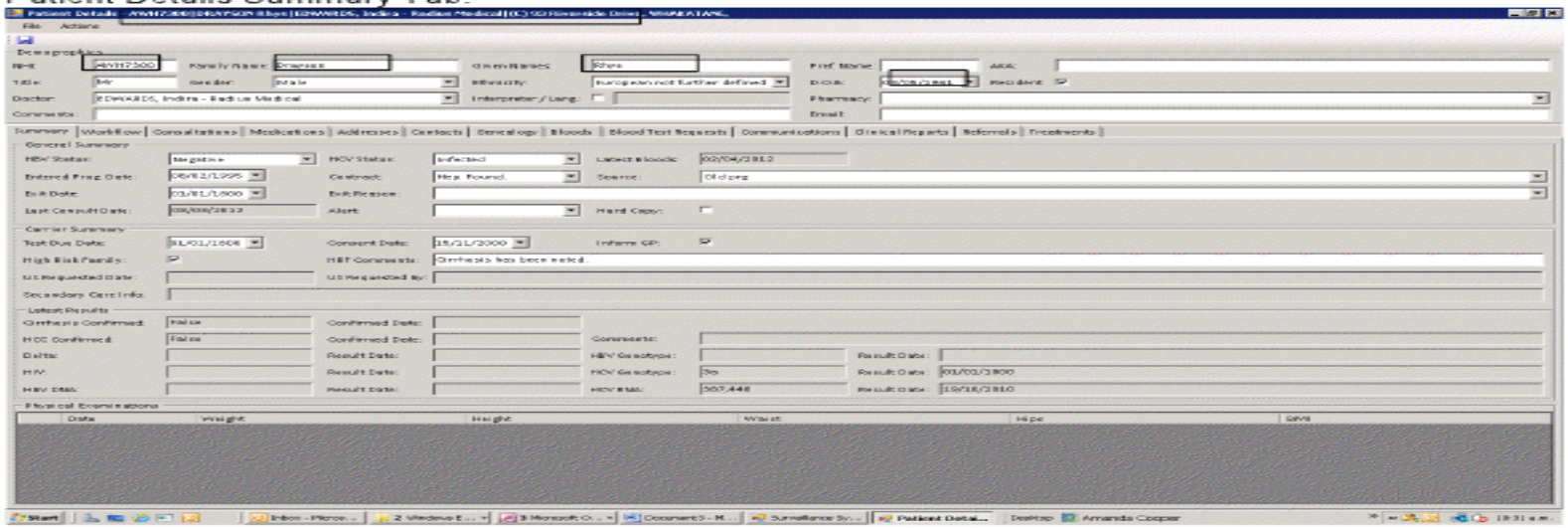
National HBV Surveillance Program

- Contracted to Hepatitis Foundation since 2002
- Still GP-based but community nurse available to chase repeated nonresponders to recall
- Facilitated collection
  - Preprinted blood forms or HepBFree stickers
- Central database (updated SQL)
  - ↑ Efficiency
  - ↑ Quality assurance; ↑ effectiveness analysis

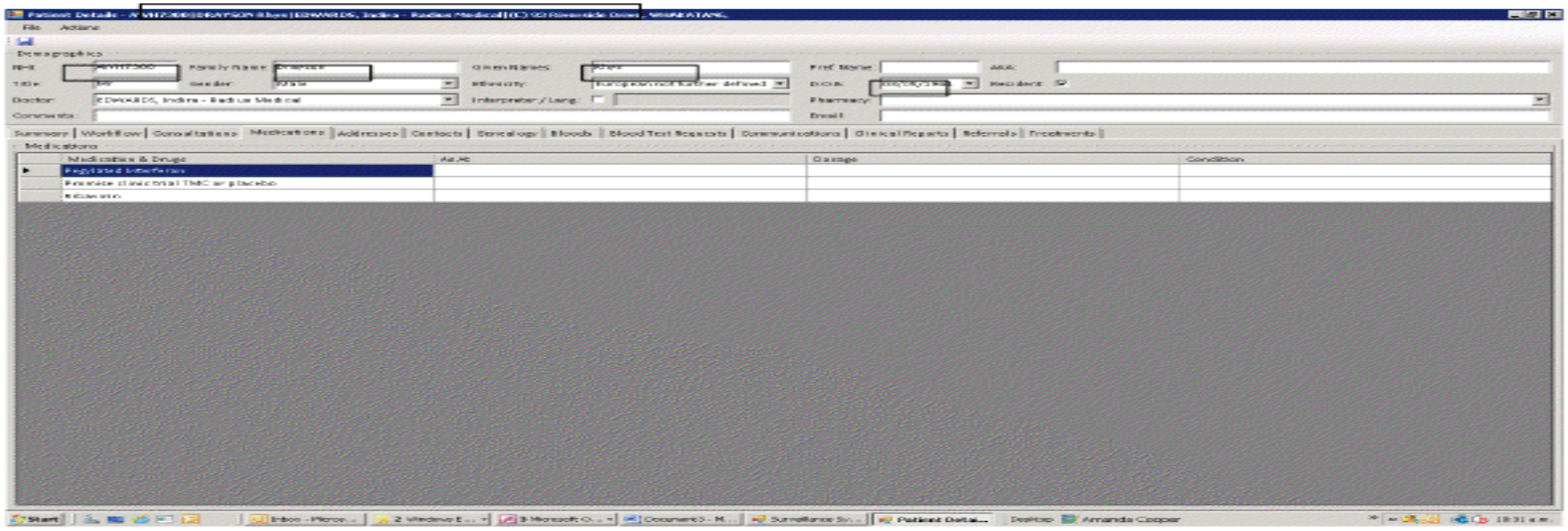
Patient Search Screen:



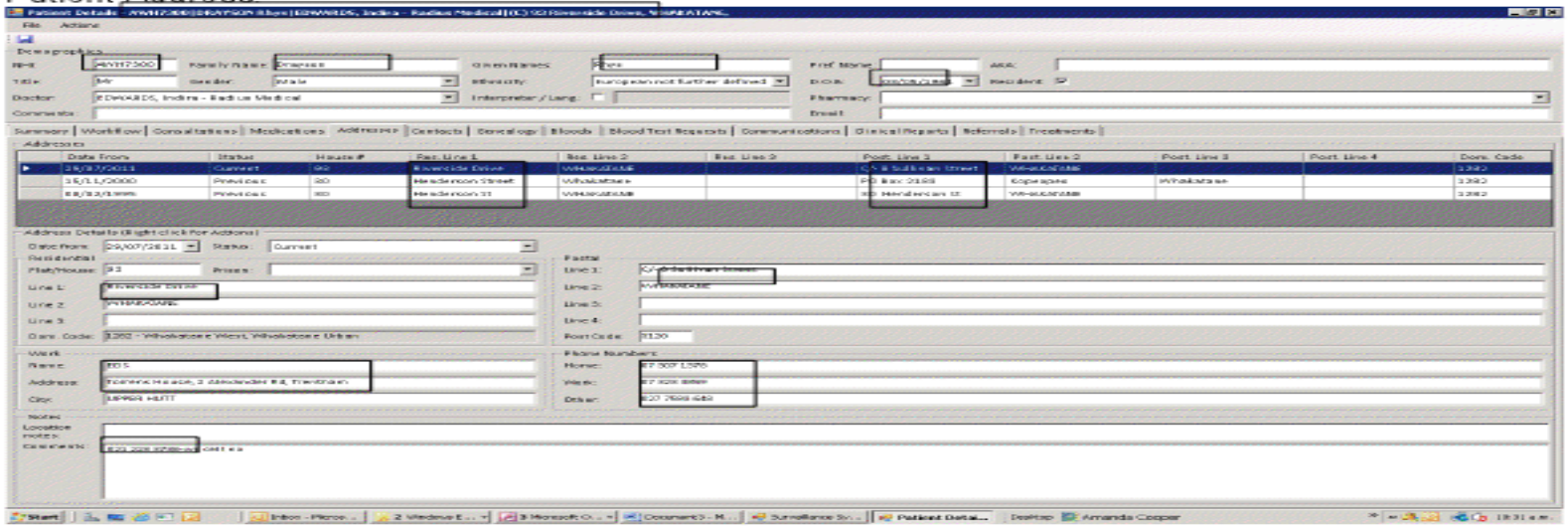
Patient Details Summary Tab:



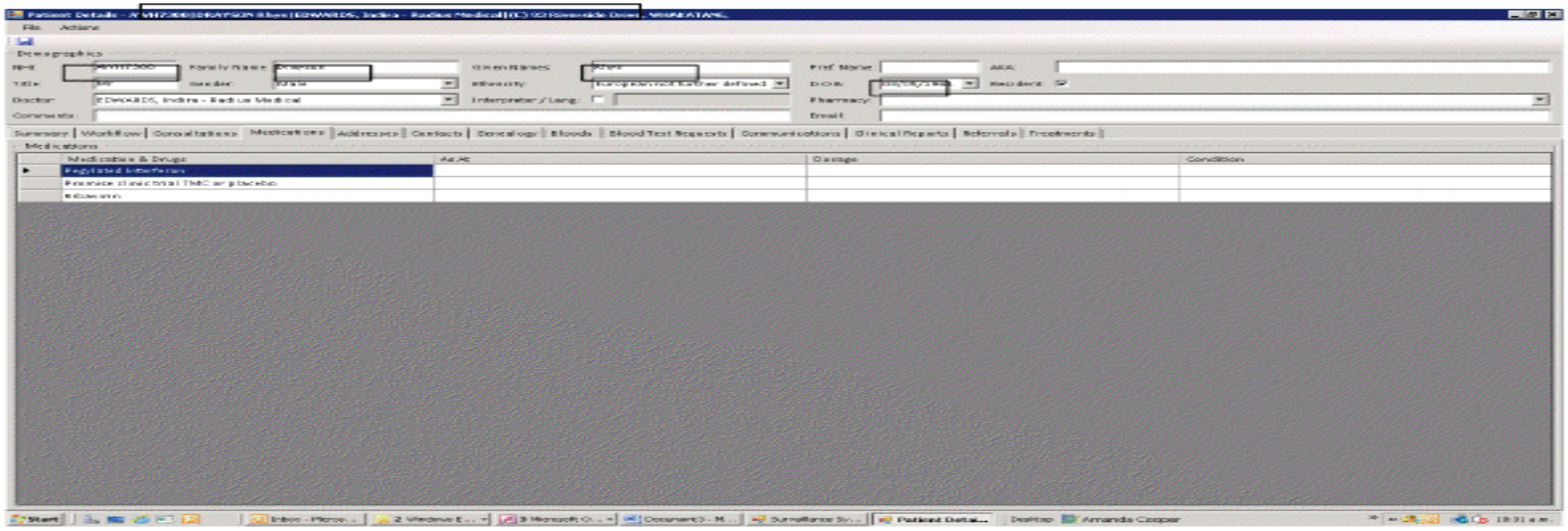
Patient Medication tab:



Patient Address:



Patient Medication tab:



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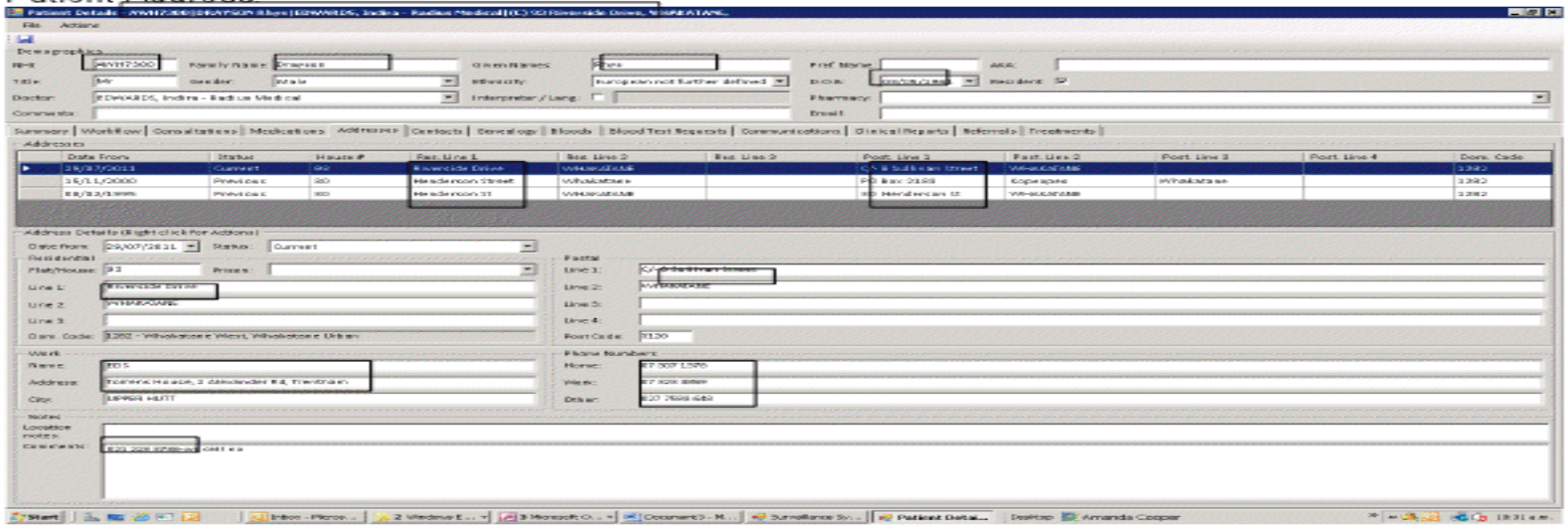
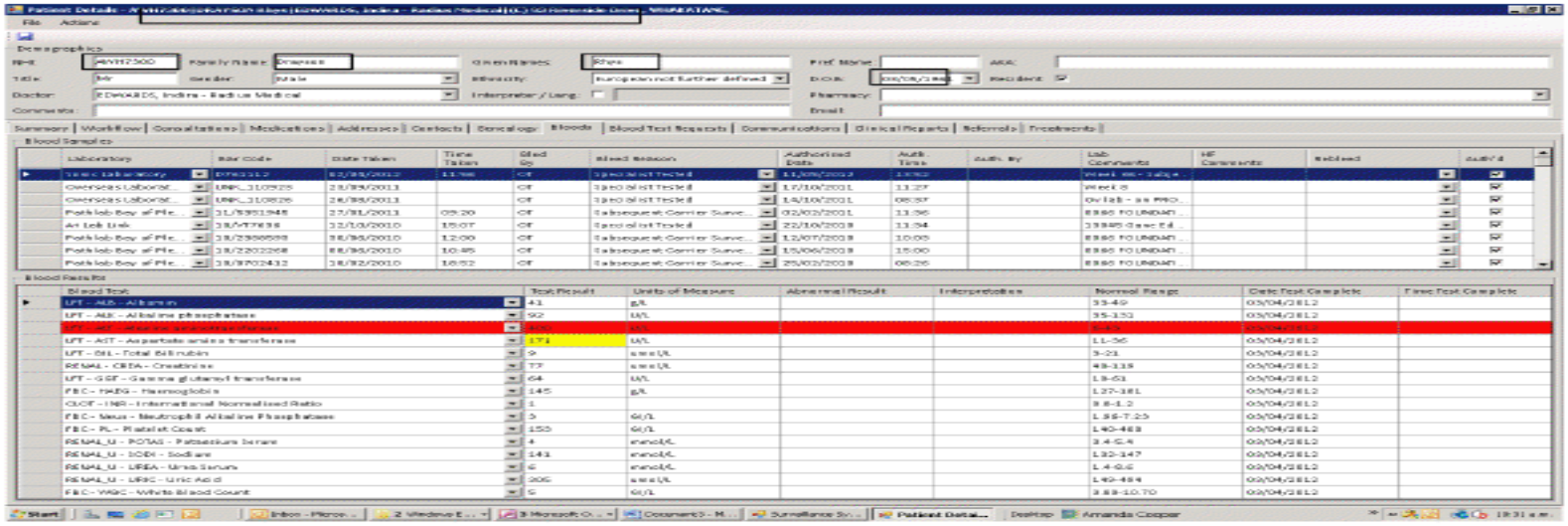


Patient Blood test results tab:



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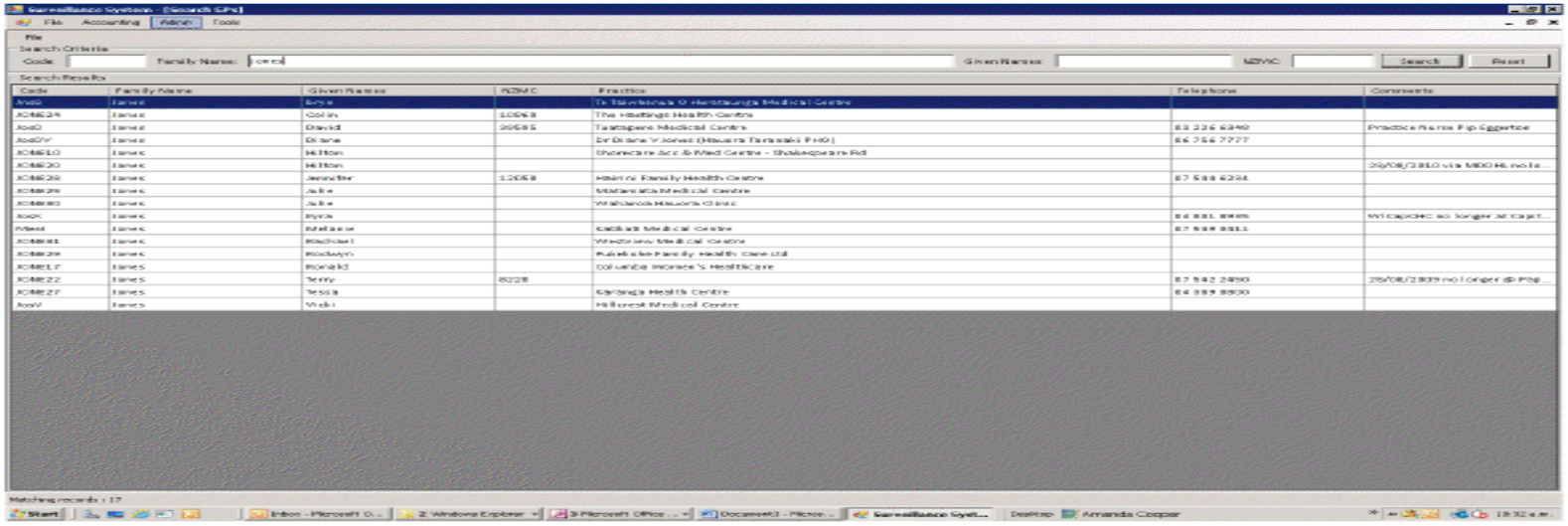

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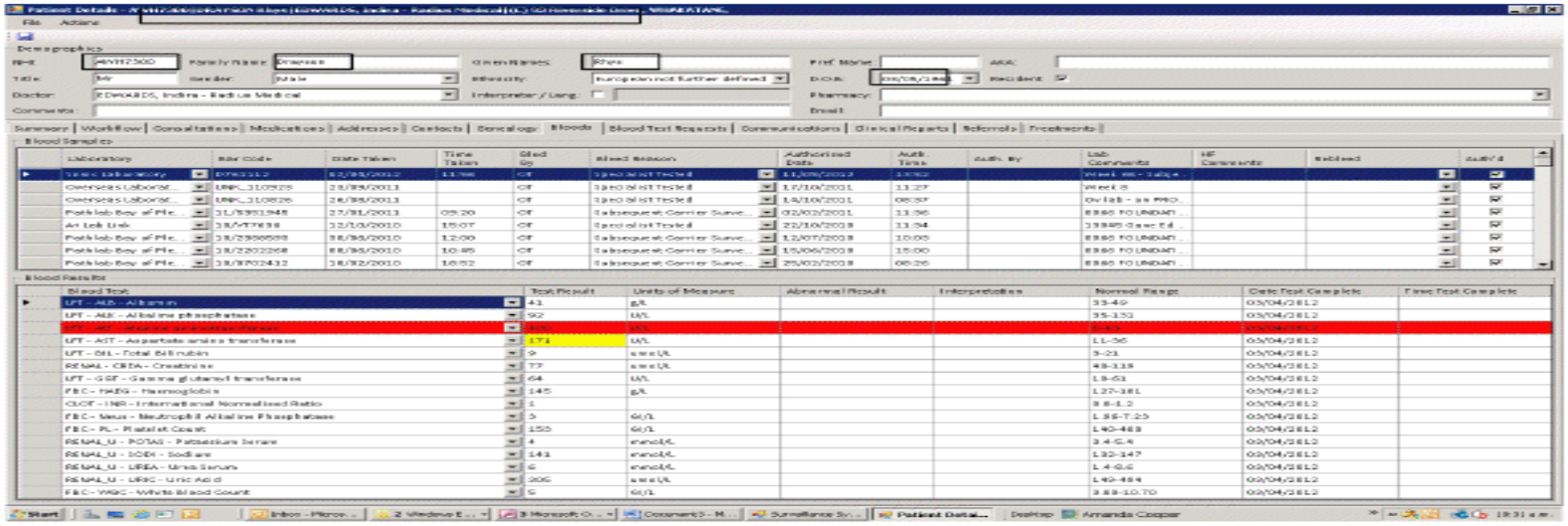

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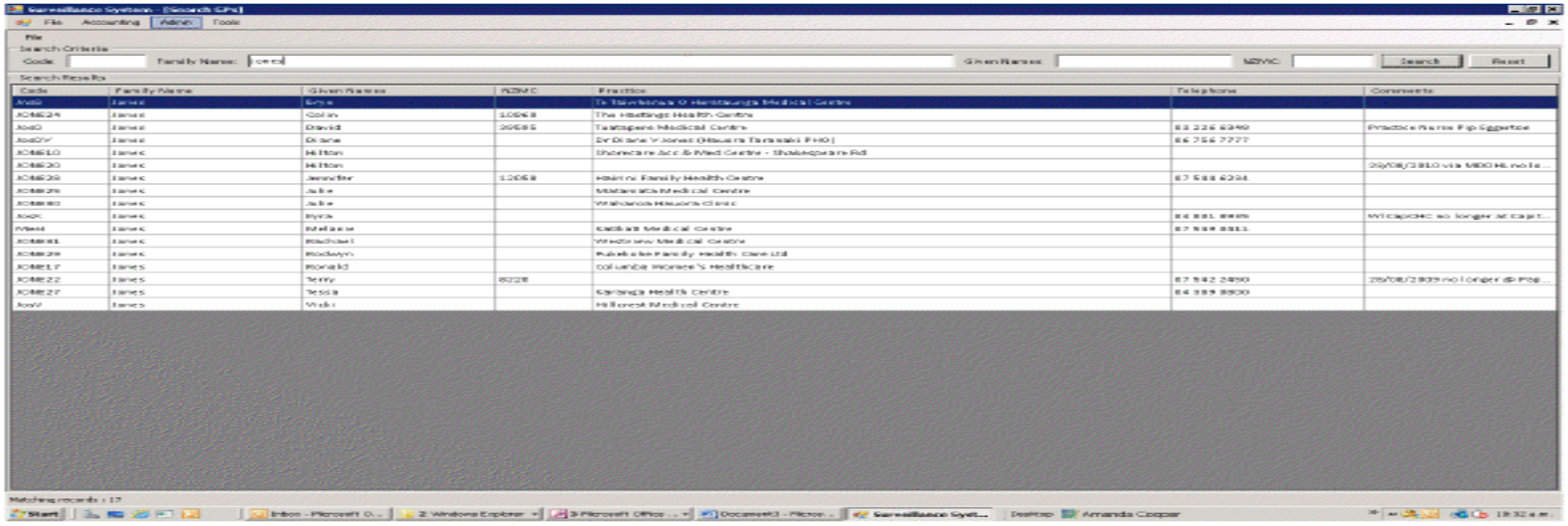

HBV – the solution

- Universal neonatal vaccination will prevent all infections
- HBV should be eradicated within next 50 years.
- For those who are already infected, long-term antiviral therapy will prevent all liver-related complications and is safe
- Early detection and long-term surveillance will improve survival

viral HEPATITIS

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