The Global Impact of Viral Hepatitis and Burden of Disease in Resource Limited Settings

Brian Montague, DO MS MPH
Assistant Professor of Medicine
Division of Infectious Diseases

Clinical Case

- 18 year old Ugandan female, no prior medical history presented with 3-4 week history of increased abdominal girth and RUQ pain. She has no known hx of hepatitis. She was anicteric. Moderate ascites was noted on exam. Liver was grossly enlarged with marked firmness on palpation. Hepatitis B surface antigen was positive. Liver ultrasound confirmed presence of ascites, as well as a large mass in the liver.

BURDEN OF DISEASE

TRANSMISSION AND PREVENTION
MANAGING CHRONIC HEPATITIS

Disease Priorities: Where is Hepatitis?

Recent "Priority" Areas

- HIV
- Malaria
- TB

NCDs

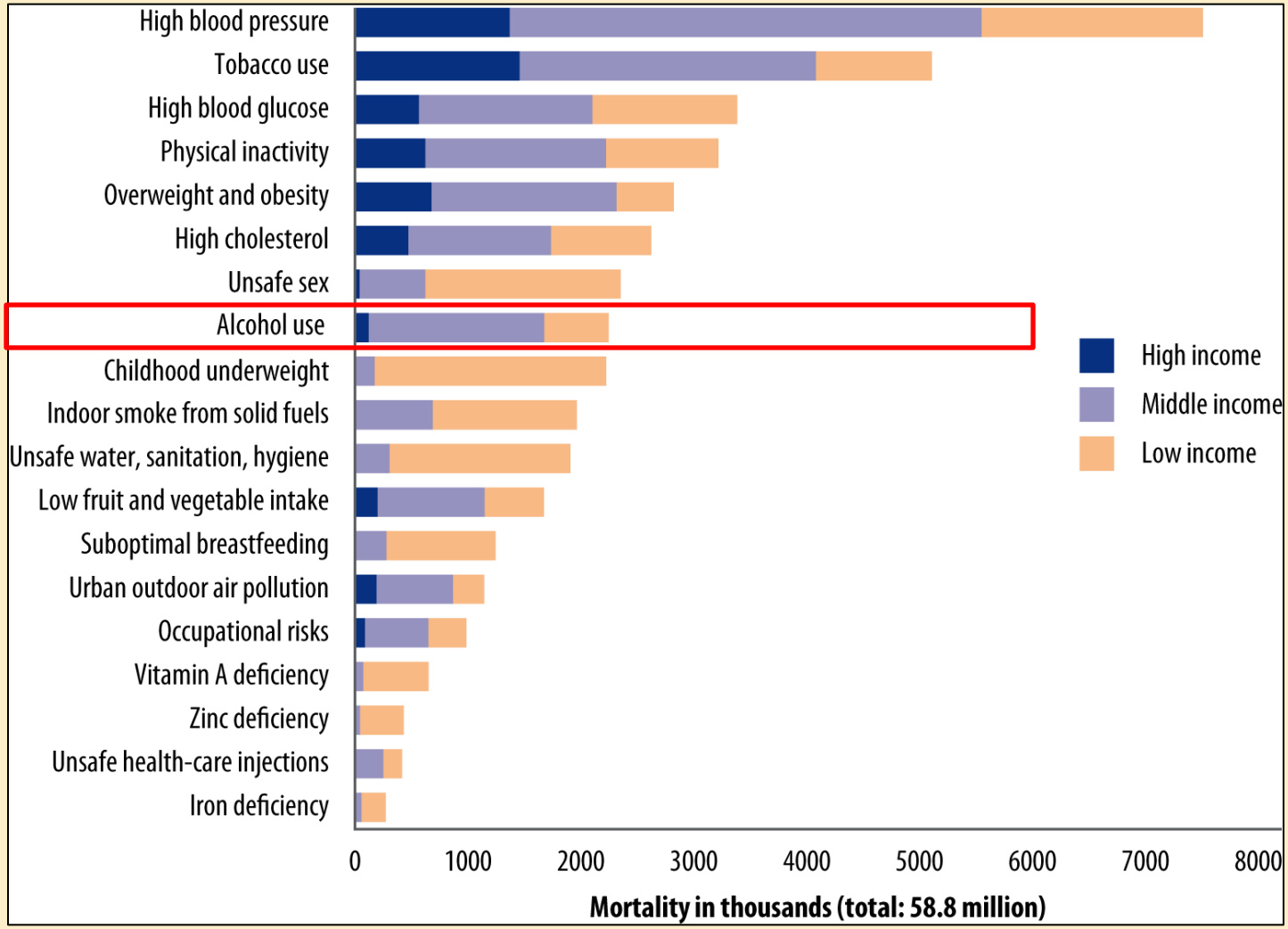
- Ischaemic and hypertensive heart disease
- Stroke
- Rheumatic heart disease
- DM
- COPD
- Cancers
- Depression and major psychoses
- Road traffic accidents
- Maternal and perinatal mortality
- Malnutrition
- ...

Neglected Tropical Diseases*

- Buruli Ulcer
- Chagas disease(American trypanosomiasis)
- Cysticercosis
- Dengue/dengue haemorrhagic fever
- Dracunculiasis (guinea-worm disease)
- Echinococcosis
- Fascioliasis
- Human African trypanosomiasis
- Leishmaniasis
- Leprosy
- Lymphatic filariasis
- Onchocerciasis
- Rabies
- Schistosomiasis
- Soil transmitted helminthiasis
- Trachoma
- Yaws
- Podoconiosis
- Snakebite
- **Other 'neglected' conditions:**

*WHO

Deaths attributed to 19 leading factors, by country income level, 2004



http://www.who.int/healthinfo/global_burden_disease/global_health_risks/en/index.html

Liver Disease Associated Mortality

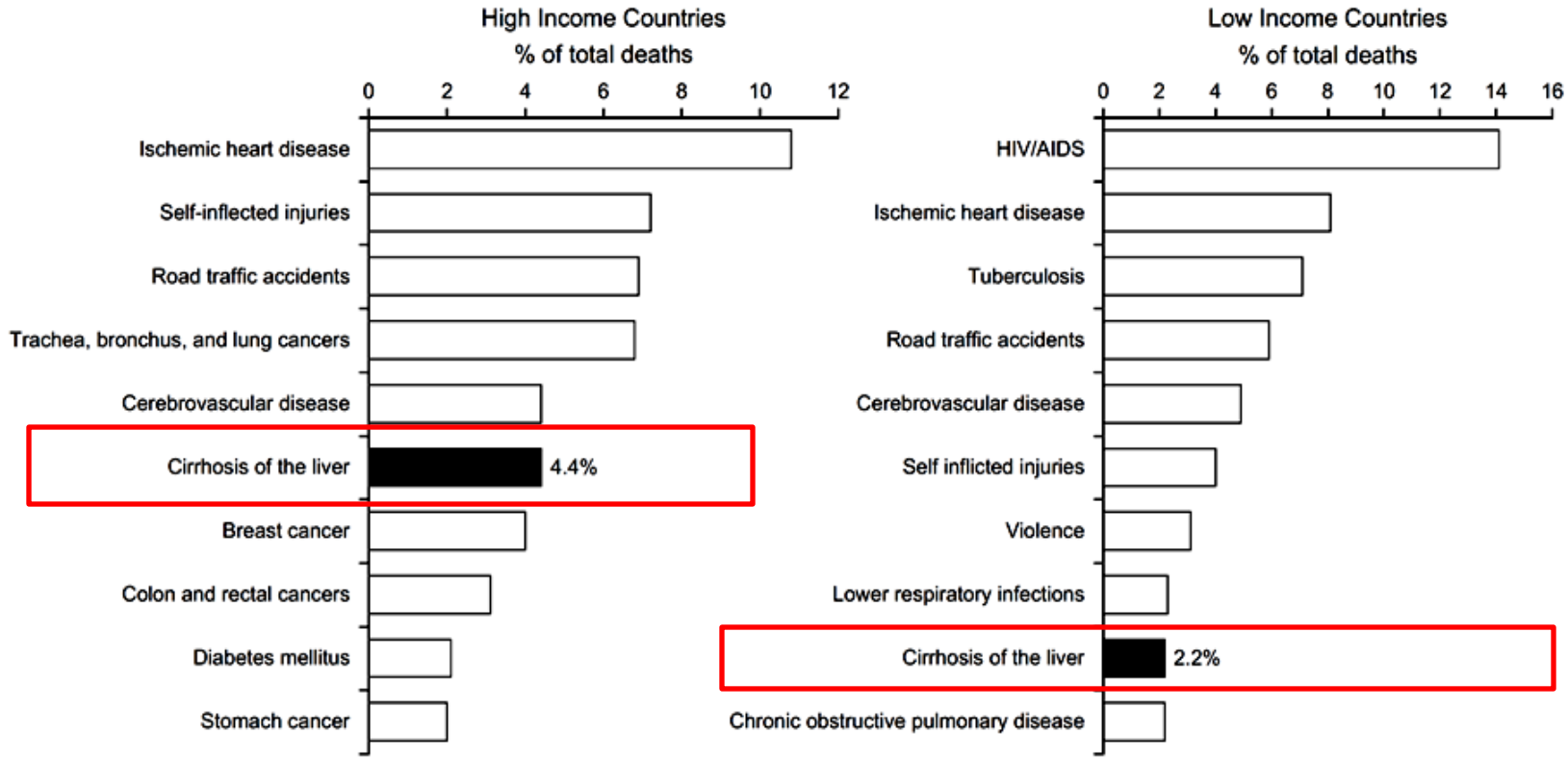


Fig.1. The 10 Leading Causes of Death in Adults Ages 15 to 59, by Broad Income Group, 2001. (*Adapted from* Mathers C, Lopez A, Murray C. of disease and mortality by condition: data, methods, and results for 2001. In: Lopez A, Mathers C, Ezzati M, et al, editors. Global burden of risk factors. Washington (DC): Oxford University Press and the World Bank; 2006. p. 45–93; with permission of Oxford University Press, 2006.)

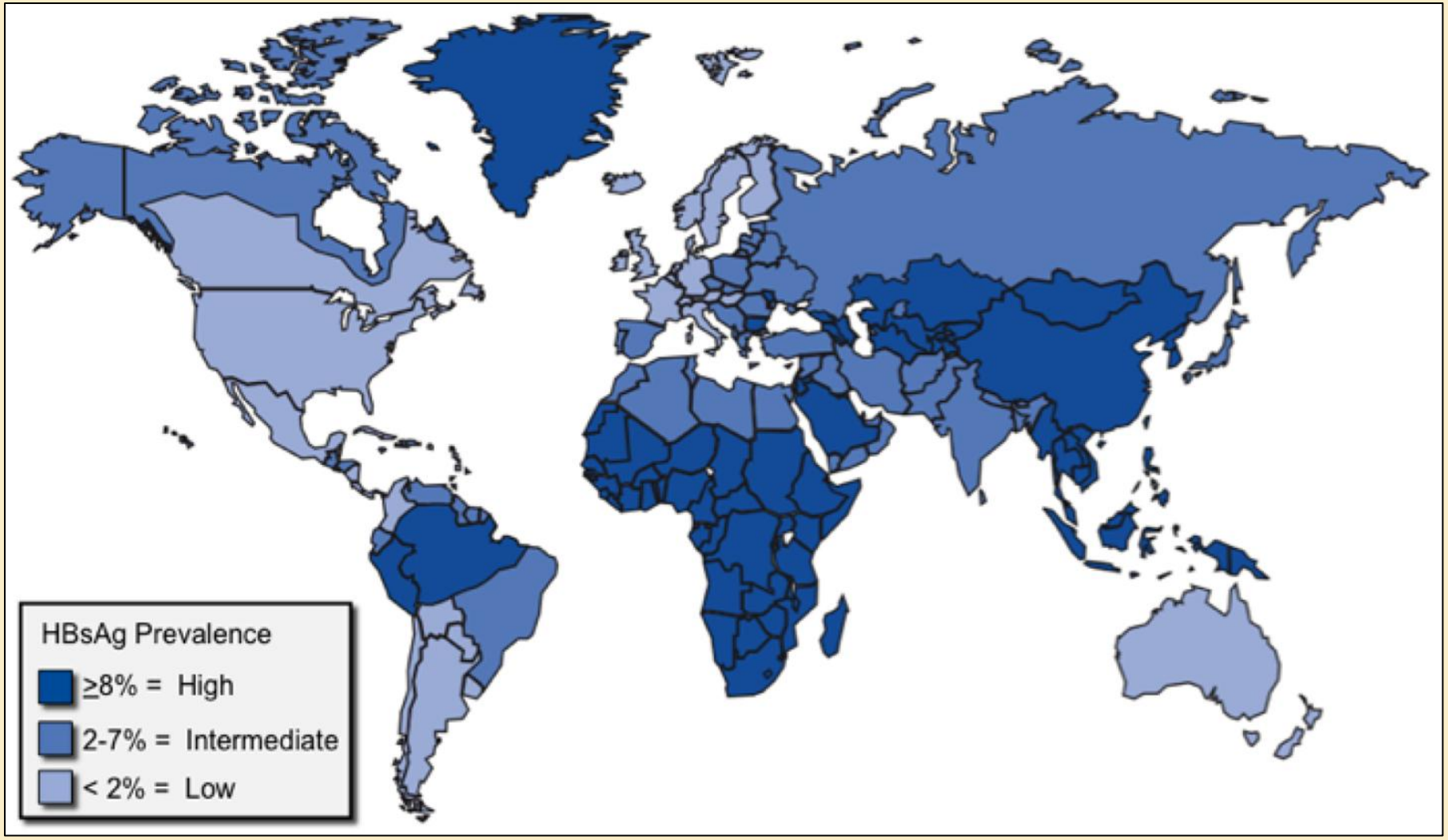
Lim & Kim. Clinics in Liver Disease 2008; 12(4):L733-746

Mortality of Vaccine Preventable Diseases

Diseases	Deaths < 5 years of age (thousands)	Deaths Total (thousands)
Diseases for which vaccination is part of most immunization schedules		
Measles	540	610
Hib	386	386
Pertussis	294	294
Tetanus	198	213
Yellow Fever	15	30
Diptheria	4	5
Polio	<1	<1
Hepatitis B	**<1**	**600**
Diseases for which a licensed vaccine is available		
Japanese encephalititis	5	14
Meningococcal	10	26
Rotavirus	402	449
Penumococcal	716	1612
Total Deaths from All Causes	10468	57029

http://www.who.int/immunization_monitoring/burden/estimates_burden/en/index.html

Global Distribution of Hepatitis B



Hwang and Cheung NAJMS. 2011;4(1):7-13

Global Distribution of Hepatitis C

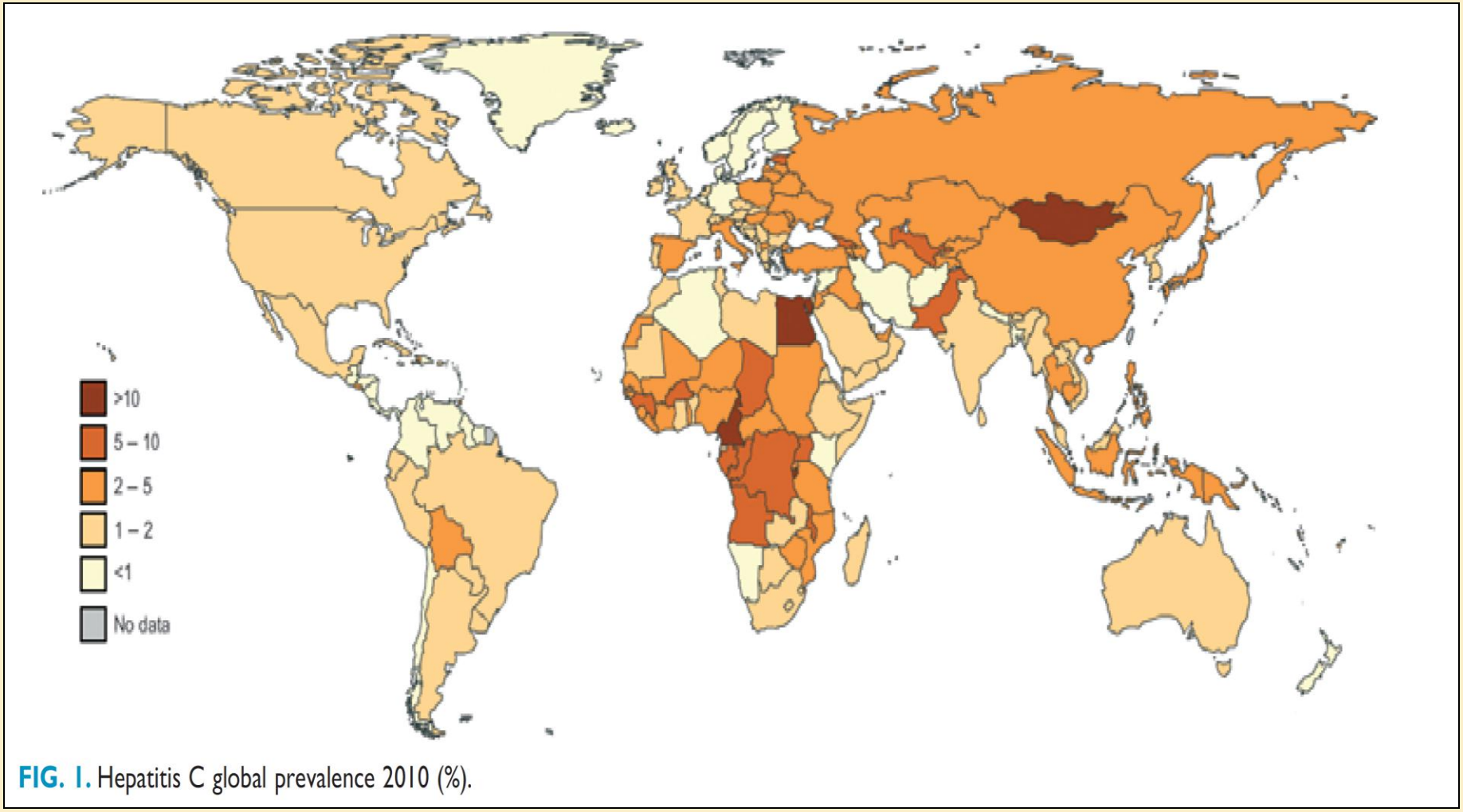


FIG. 1. Hepatitis C global prevalence 2010 (%).

Lavanchy. Clin Microbiol Infect 2011; 17: 107–115

Life Expectancy 2005-2010

Country or Area	Value
Brazil	72.3
Sub-Saharan Africa	51.5
Central African Republic	46.9
Gambia	55.8
Kenya	54.2
Uganda	52.4
India	63.5
Pakistan	66.3
China	73.0
Japan	82.7
Republic of Korea	79.4
Thailand	68.8
France	81.2
United Kingdom	79.4
United States of America	79.2

http://data.un.org/Data.aspx?q=uganda&d=PopDiv&f=variableID:68;crID:800

Shanghai Hepatitis B Cohort

Table 1 Age at diagnosis and duration of follow-up time of 280 subjects[†]

Chronic hepatitis B groups	No.	Min.	Max.	Mean	SD	*P*-value[‡]
Age at diagnosis (years)						
Without CC	244[§]	12.1	71.2	34.0	10.4	0.041
With CC	34	22.0	71.6	37.9	10.9	
Duration of follow up (years)						
Without CC	246	0.4	17.1	13.5	2.3	0.004
With CC	34	1.9	18.6	11.0	4.4	

[†]Final visit refusals included where other follow-up data were available. [‡]*P*-value from Student's *t*-test. [§]Two missing values. CC, compensated cirrhosis.

Xu. Shanghai Hepatitis Cohort *Journal of Gastroenterology and Hepatology* (2003) **18,** 1345–1352

Shanghai Hepatitis B Cohort

Table 2 General demographic and disease characteristics of patients at baseline or final visit

Features	CHB without CC No.	CHB without CC %	CHB with CC No.	CHB with CC %	*P*-value†
			Baseline		
Total	246	100.0	34	100.0	
Male	206	83.7	27	79.4	0.53
HBsAg(+) and HBeAg(+)‡	91	37.0	16	47.1	0.26
			Final visit		
Combined infection§					
HCV	7	4.3	0	0.0	
HDV	14	8.6	2	10.5	
HCV and HDV	1	0.0	0	0.0	
HBsAg(+) and HBeAg(+)	26	10.6	10	29.4	0.00
Reason for death					
Decompensated cirrhosis	12	48.2	7	53.9	
Liver cancer	7	28.2	3	23.1	
Other cancer	0	0.0	2	15.4	
Other disease	6	24.0	1	7.7	
All deaths	25	100.0	13	100.0	

†*P*-value from χ^2 test. ‡Measured at entry. §Measured at final observation among 181 responded subjects (162 without CC and 19 with CC). CC, compensated cirrhosis; CHB, chronic hepatitis B; HBeAg, hepatitis B early antigen; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HDV, hepatitis D virus.

Xu. Shanghai Hepatitis Cohort *Journal of Gastroenterology and Hepatology* (2003) **18,** 1345–1352

Do People Live Long Enough to Experience Complications?

Table 3 Rate of non-progression to decompensated cirrhosis (DC), hepatocellular carcinoma (HCC), and death

Chronic hepatitis B group	Patients with events/*n*	Rates (PYO)	95% confidence interval[†]	Mean time to event (years)	5-year non-progression rate	10-year non-progression rate	15-year non-progression rate
DC							
Total	32/279[‡]	9.1	4.0–17.1	17.1	0.95	0.92	0.85
Without CC	20/245[‡]	6.3	2.2–13.1	16.3	0.97	0.95	0.89[§]
With CC	12/34	35.6	25.1–49.8	13.8	0.82	0.64	0.59
HCC							
Total	12/279[‡]	3.4	0.6–8.8	18.1	0.98	0.96	0.95
Without CC	9/245[‡]	2.8	0.6–8.8	16.8	1.00	0.97	0.96[§]
With CC	3/34	8.2	3.4–15.8	17.3	0.94	0.90	0.90
Death							
Total	38/280	10.6	5.4–19.7	17.0	0.94	0.90	0.84
Without CC	25/246	7.6	3.4–15.8	16.1	0.95	0.93	0.88[§]
With CC	13/34	35.2	24.3–48.7	13.8	0.85	0.69	0.56

[†]Calculated from Poisson distribution. [‡]One missing value. [§]Log-rank test for rates of non-progression during whole study period: $P = 0.0888$ for HCC, $P = 0.0000$ for DC and $P = 0.0000$ for death. CC, compensated cirrhosis; PYO, per 1000 person-years of observation.

Hepatitis C

- Natural History
  - Approximately 85% of those infected remain chronically infected
  - Median time to cirrhosis 30 years with significant variability based on lifestyle and other factors

Prognosis with Hepatitis C

- German cohort
- 838 patients
- Followed for 50.2 +/-26.9 months (range, 6-122)

TABLE 1. Duration of Infection and Age at Study Entry in Patients With and Without Histological Evidence of Cirrhosis, Fibrosis, and Chronic Hepatitis on Initial Liver Biopsy and in Patients With and Without Development of HCC During Follow-up

	Number	Duration of Infection (yr)	Age at Entry (yr)
Stage*			
Neither fibrosis nor cirrhosis	362	9.0 ± 6.8	46.3 ± 14.1
Fibrosis	88	13.1 ± 6.4	55.7 ± 11.7
Cirrhosis	130	16.2 ± 7.9	57.8 ± 10.0
Inflammatory activity†			
No hepatitis/minimal hepatitis	68	13.4 ± 9.6	47.3 ± 13.9
Chronic hepatitis	512	11.8 ± 7.4	50.7 ± 13.8
Sum of patients with initial liver biopsy	580	11.3 ± 7.7	50.3 ± 13.9
HCC*			
HCC during follow-up	17	21.8 ± 6.2	62.2 ± 11.6
No HCC during follow-up	821	10.1 ± 7.5	49.1 ± 14.6
Sum of all patients	838	10.3 ± 7.6	49.4 ± 14.6

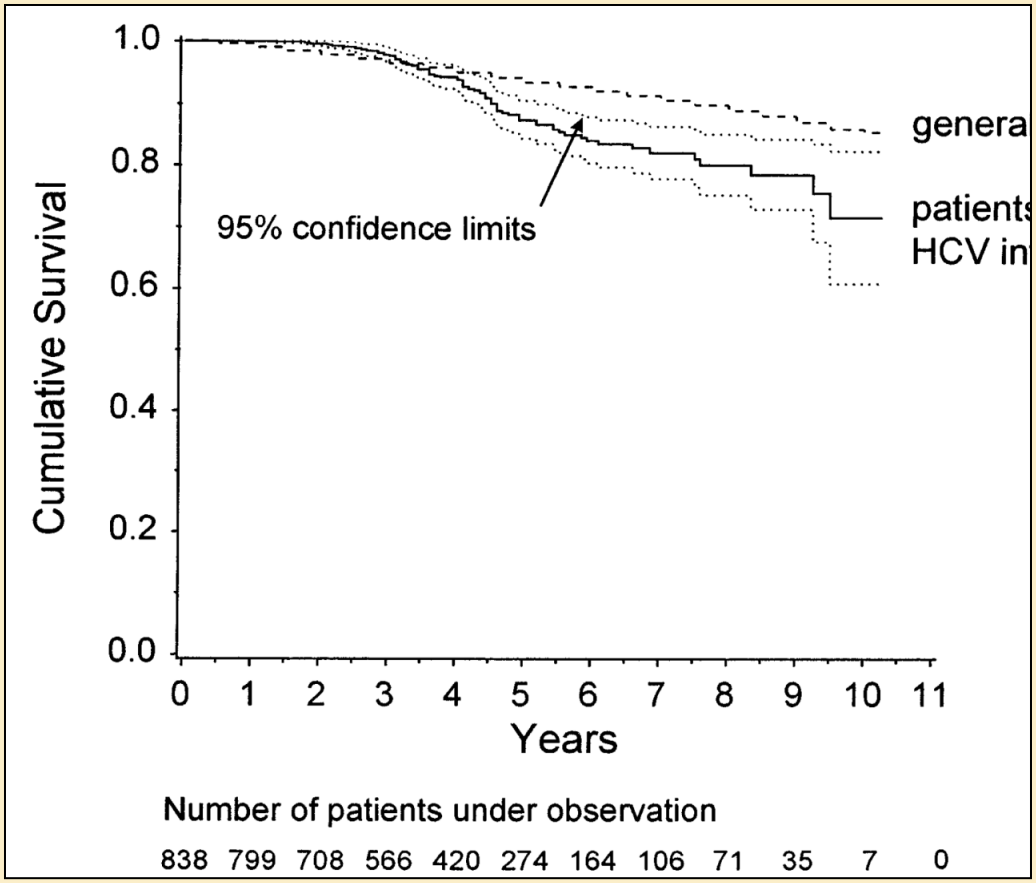
NOTE. Data are shown as mean values ± SD.

*$P < .001$ by ANOVA for comparing both age at entry and disease duration for different stages of liver disease and for patients with and without development of HCC.

†$P < .05$ for age at entry and $P > .05$ for duration of infection when the latter analysis was performed for patients with histology of chronic hepatitis versus patients without histological evidence of chronic hepatitis.

Niederau eta l. HEPATOLOGY Vol. 28, No. 6, 1998

Survival Impact of Hepatitis C



? Slower disease progression in children but studies in this area are sorely lacking

Niederau eta l. HEPATOLOGY Vol. 28, No. 6, 1998

Geographic Variability

Asia

- Largely vertical transmission of Hepatitis B
- Iatrogenic transmission of Hepatitis C

Africa

- Significant early childhood transmission of Hepatitis B
- Iatrogenic transmission of Hepatitis C

- Earlier onset of hepatocellular carcinoma
  - Assoc with environmental aflatoxin exposure

Natural history data from Africa is very limited.

BURDEN OF DISEASE

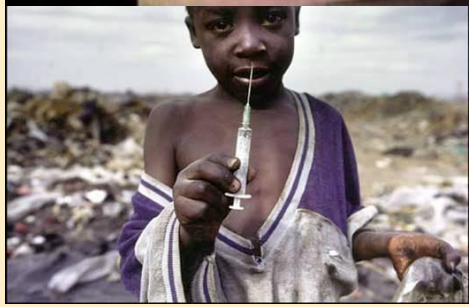
TRANSMISSION AND PREVENTION

MANAGING CHRONIC HEPATITIS

Transmission of Hepatitis

- Fecal/Oral
  - Hepatitis A
  - Hepatitis E

  } Sanitation and hygeine
- Vertical
  - Hepatitis B, less commonly D
- Close Contacts/Sexual
  - Hepatitis B, D, less commonly C
- Iatrogenic (injections, transfusions)
  - Hepatitis B and C



Safety of the Blood Supply

- Globally, approximately 80 million units of blood are donated each year.
  - Of this total, 2 million units are donated in sub- Saharan Africa
- In 2004, blood collections in most of the 14 PEPFAR-supported countries did not satisfy clinical demand.
  - Collections often were coordinated by hospital-based services that frequently relied on paid donors or replacement donors
  - HIV screening of donor blood often performed in non-standardized laboratories without quality assurance
- Recommendations for hepatitis screening of blood supply
  - Screening for Hepatitis B by HepBSAg
  - Screening for Hepatitis C either by antibody or by antigen/antibody combination

MMWR. 2008;57:1273-1277

Screening Strategies

Table 2 Number of reactive donations using different testing strategies in South Africa

Disease marker	NAT	Serology	Total
HIV	3183	3121	3205
HBV	2139	1979	2210
HCV	140	222	226

Serology Only: 22 samples for HIV, 71 for HBV, 86 for HCV

Vermeulen & Reddy ISBT Science Series (2010) 5, 308–313

WHO Global Database on Blood Safety

Africa

- 95% of African countries were testing 100% of units for HIV
- 83% of countries were testing for HBV
- 53% for HCV,

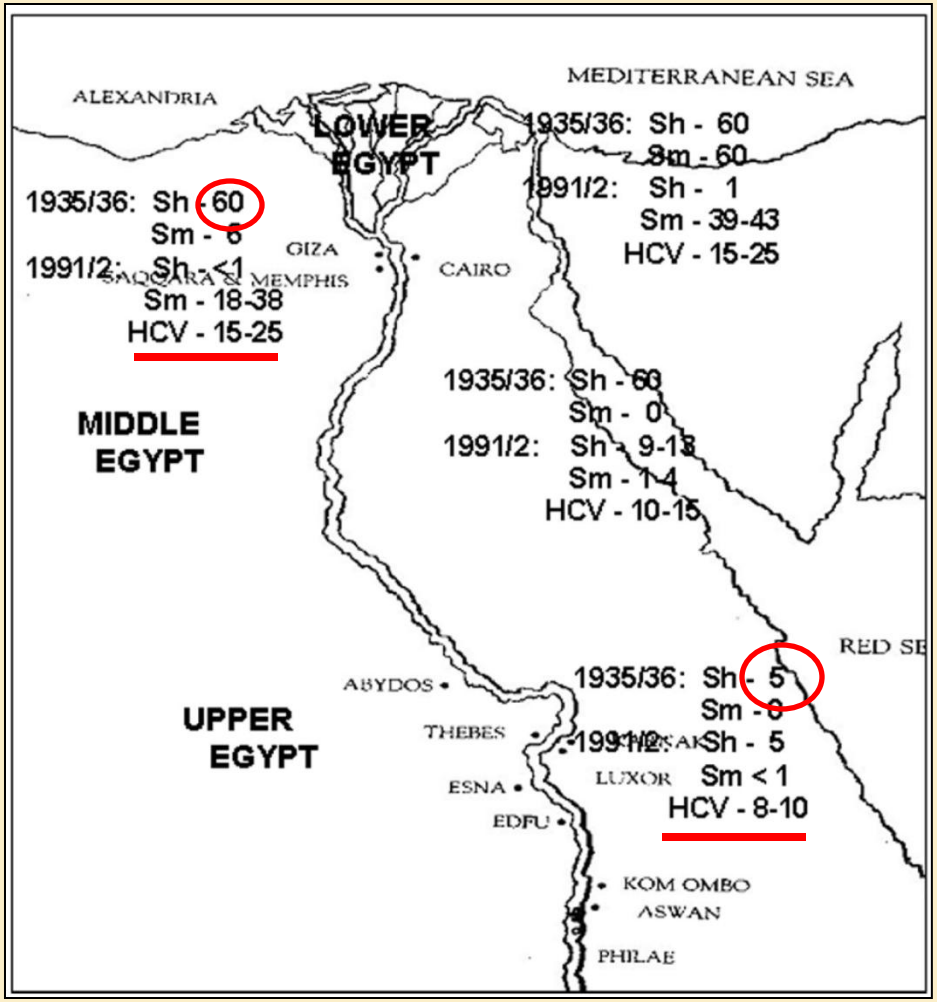
- Goal is to have 100% of the blood screened by 2012 for all of these TTI markers
  - Of the 155 countries that reported performing 100% screening for HIV, only 71 screen in a quality-assured manner defined as:
    - laboratories follow documented standard operating procedures
    - Employment of an external quality assessment scheme.

Asia

- In Asia all blood is 100% tested for HIV and HBV (except in Indonesia which tests 97%)
- HCV testing has not been initiated in all countries

Iatrogenic Spread of Disease

- Egypt: Hepatitis C
  - From the 1950s until the 1980s, the Egyptian MOH large schistosomiasis control campaigns using intravenous tartar emetic
  - Disposable syringes not available during the campaigns and sterilization was inadequate



Strickland HEPATOLOGY 2006;43:915-922

Infections Attributable to Unsafe Injections

Table 2. **Estimated proportion of unsafe injections and estimated number of hepatitis B (HBV), hepatitis C (HCV), and human immunodeficiency virus (HIV) infections, by region**

Region	Proportion of unsafe injections, *P*(u)	Estimated no. of infections[a]					
		HBV		HCV		HIV	
		n = 1	*n* = 2	*n* = 1	*n* = 2	*n* = 1	*n* = 2
Established market economies	0	0	0	0	0	0	0
Latin America and the Caribbean	NA	NA	NA	NA	NA	NA	NA
Former Socialist Economies of Europe	0.15	446 278	892 555	60 772	121 543	11 907	23 814
Middle Eastern crescent	0.15	520 011	1 040 022	70 813	141 625	122	243
India	0.50	3 130 524	6 261 047	405 430	810 859	4 312	8 624
China	0.50	2 078 559	4 157 117	1 136 743	2 273 485	286	572
Sub-Saharan Africa	0.50	780 052	1 560 104	254 946	509 892	51 208	102 415
Other Asian countries and Pacific islands	0.50	1 255 118	2 510 235	410 212	820 424	12 850	25 699
Total		**8 210 541**	**16 421 081**	**2 338 915**	**4 677 829**	**80 684**	**161 367**

[a] *n* = No. of injections received per person per year; NA = not available.

Kane et al. Bull WHO 199 77(10)

Vaccination

- Hepatitis B
  - Effective vaccine with 3 dose series
  - Standard and accelerated vaccine schedules
  - Birth dose vaccine

- Limitations
  - Potential reduced efficacy in immunocompromised and ESRD patients
  - Cold chain
  - Out of hospital births
- In Development
  - Trials double dose vaccine
  - Vaccines with increased immunogenicity

Immunogenicity of HepB Vaccine in Patients with HIV

•Study of antibody response to hepatitis B vaccine comparing patients with "high" CD4 count (>200) to low CD4 count (<200). No protective response noted in any persons with CD4 < 50

Table 2: Post vaccination sequential anti HBsAb titers in different groups

Stages	Mean ± SD in group IA patient	Mean ± SD in group IB patients	Mean ± SD in group II normal controls
Baseline B	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
Before 2nd dose (C)	205 ± 613	1 ± 4	0.00 ± 0.00
After 2nd dose (D)	1181 ± 2912	26 ± 49	118 ± 397
Before 3rd dose (E)	524 ± 1478	40 ± 90	225 ± 317
After 3rd dose (F)	8834 ± 14136	462 ± 814	16906 ± 21301
Statistical Significance	**p**	**p**	**p**
	B/C > 0.05, BD < 0.05 B/E > 0.05 B/F < 0.01*	B/C > 0.05 B/D > 0.05 B/E > 0.05 B/F < 0.05	B/C > 0.05 B/D > 0.05 B/E < 0.01* B/F < 0.01*

Therapeutic titers defined as > 100

Parischa et al. BMC Infectious Diseases 2006, ***6:65***

Vaccines in Development

- Hepatitis E
  - No currently approved vaccine
  - Trial Nepal 2007 showed efficacy in predominantly young male cohort
  - Chinese vaccine in phase 3 trials
- Hepatitis C
  - Genetic diversity and mutability of virus has hindered vaccine development
- Hepatitis D
  - Limited study
  - Given that infection requires preexisting hep B, hep B vaccination primary prevention target

Vaccination

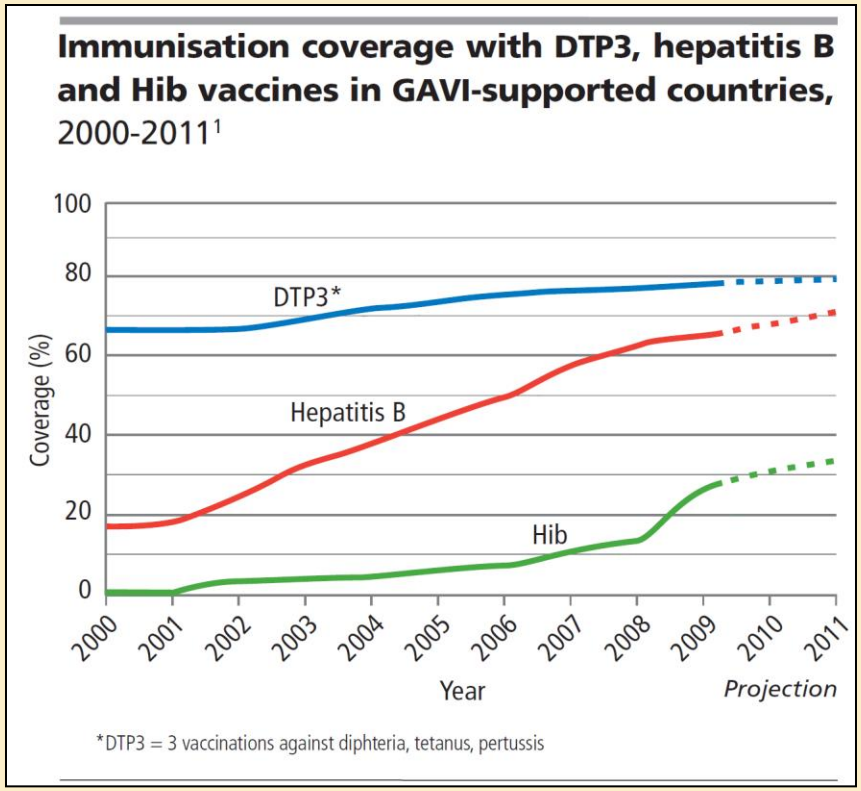
- Hepatitis A
  - Effective vaccine with 2-dose series
  - Standard and accelerated vaccine schedules (when given in combination dose with hep B)

- Limitations
  - Mostly of benefit to travellers given exposure nearly ubiquitous in resource limited settings
  - Infection generally mild and transient when contracted early in life (analogous to Varicella)

GAVI

- Initially provided support for combination vaccines only
- Works with recipient countries with shared financing model

- New initiative: New and underused vaccines support (NVS)
  - Including hepatitis B & Hib monovalent vaccine for support of birth dose vaccine



http://www.gavialliance.org/resources/GAVI_Alliance_Feb_2011.pdf

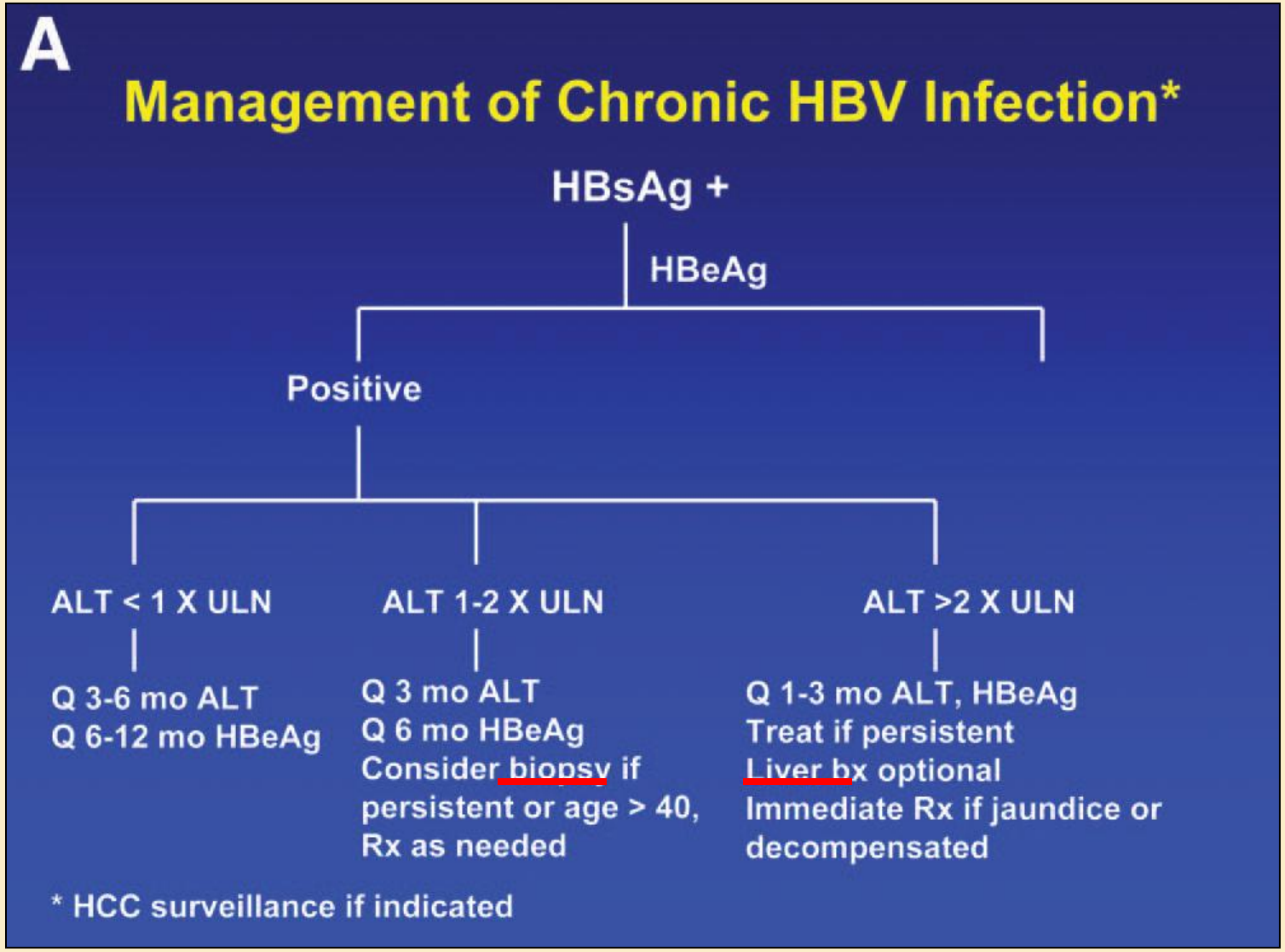
BURDEN OF DISEASE
TRANSMISSION AND PREVENTION

MANAGING CHRONIC HEPATITIS

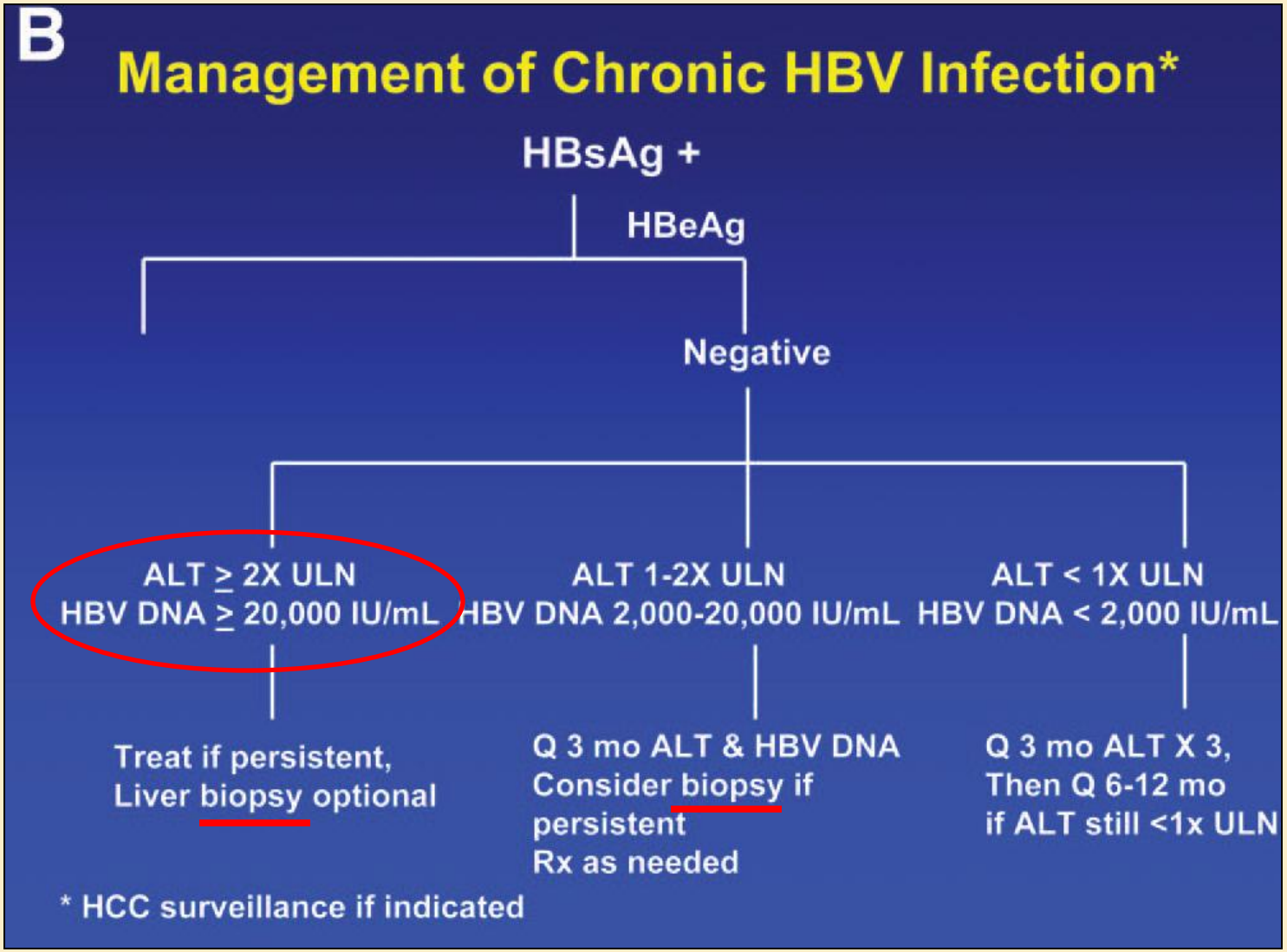
Hepatitis B

- Criteria for Treatment
  - Active inflammation by ALT or by biopsy
  - Confirmed cirrhosis
- Treatment options
  - Interferon
  - Nucleotide analogs (TDF,Entecavir)
- Treatment success
  - ALT normalization
  - Virologic suppression
- Treatment Endpoint
  - E antigen conversion
  - Surface antigen conversion

AASLD Guidelines: Eag Positive



AASLD Guidelines: Eag Negative



Adapting for Resource Limited Settings

- Standard Protocols
  - ALT monitoring feasible
  - HBV DNA cost prohibitive and rarely used ($150-$200)
  - Lamivudine 1st line, but response not durable
  - Interferon feasible, but monitoring much less strict (and may be more expensive)

Hepatitis C

- Criteria for Treatment
  - Detectable HCV RNA
  - Active inflammation as measured by transaminitis or biopsy
- Treatment
  - Pegylated interferon + ribavirin (+/- small molecules)
- Monitoring with treatment
  - CBC, LFTs monthly
  - TSH q12 w
  - HCV RNA baseline, +/- 4w, 12w, q12w until tx complete
  - More frequent lab tests may be necessary if significant cytopenias or hepatic inflammation develops
- Counseling regarding ETOH use, pregnancy risk and ribavirin, etc.

Monitoring IFN/RBV Treatment

			TREATMENT								
	LAB TEST	SCREEN*	BASELINE†	WEEK 1	WEEK 2	WEEK 4	WEEK 8	WEEK 12	WEEK 16	WEEK 20	WEEK 24
VIRAL	HCV RNA										
BLOOD	Hematocrit %										
	Hemoglobin										
	INR										
	Platelets (RBC)										
	Neutrophils (ANC)										
	WBC										
ORGAN SPECIFIC	Albumin										
	Alk Phos										
	ALT										
	AST										
	Total Bilirubin										
	Total Protein										
	TSH										
SERUM	Calcium										
	Creatinine										
	Glucose										
	Potassium										
	Pregnancy										
	Sodium										
	Urea										
URINE	Urinalysis‡										

Risks Associated with Treatment

- Autoimmune thyroiditis (~15%)
- Cytopenias
  - Anemia (RBV)
  - Thrombocytopenia (IFN)
  - Neutropenia (IFN)
- Decompensated Cirrhosis
- Depression/Mania
- Severe infections

Adapting for Resource Limited Settings

- HCV quantitative RNA, if available, is expensive. Cost $160-$200.
- How often will patient be seen?
- There are 50 patients behind them in line, how much counseling will they receive?
- Can they afford the lab tests, much less the medications?

- Do the risks of treatment outweigh the benefits?

Clinical Case

- 38 year old Ugandan man, diagnosed with hepatitis B 2 years prior. Patient symptomatic with RUQ pain, no jaundice. At time of dx, elevation in ALT noted at 146. Patient started on lamivudine. ALT improved to 46 at recheck after 1 year and patient experienced some symptomatic improvement. On f/u today, he has mild RUQ pain, ALT 92. No jaundice. No stigmata of cirrhosis.

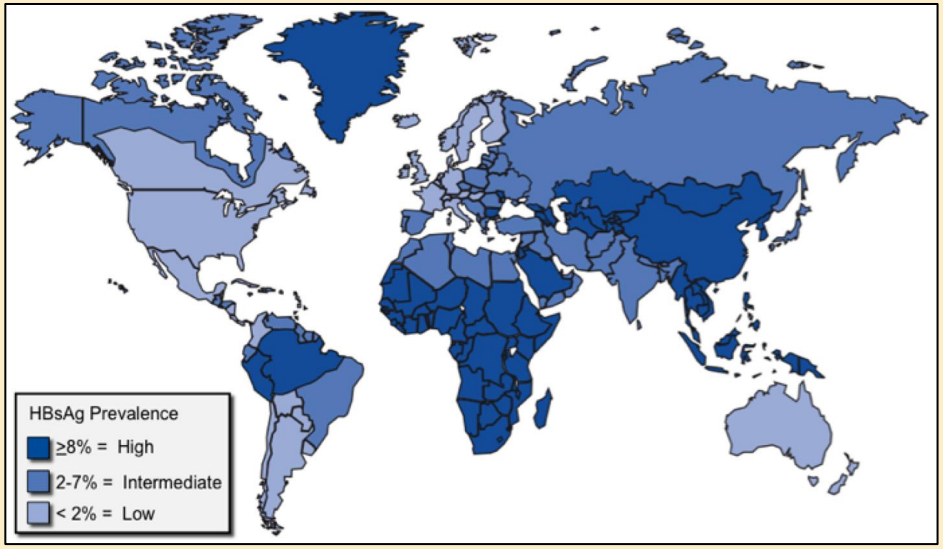
- What do you do now?

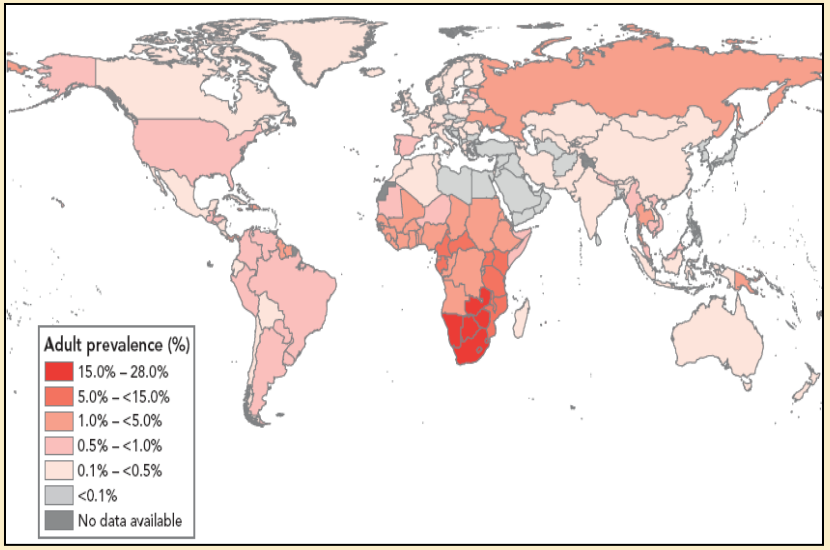
Defining Treatment Response

Table 6. Definition of Response to Antiviral Therapy of Chronic Hepatitis B

	Category of Response
Biochemical (BR)	Decrease in serum ALT to within the normal range
Virologic (VR)	Decrease in serum HBV DNA to undetectable levels by PCR assays, and loss of HBeAg in patients who were initially HBeAg positive
Primary non-response (not applicable to interferon therapy)	Decrease in serum HBV DNA by <2 $\log_{10}$ IU/mL after at least 24 weeks of therapy
Virologic relapse	Increase in serum HBV DNA of 1 log10 IU/mL after discontinuation of treatment in at least two determinations more than 4 weeks apart
Histologic (HR)	Decrease in histology activity index by at least 2 points and no worsening of fibrosis score compared to pre-treatment liver biopsy
Complete (CR)	Fulfill criteria of biochemical and virological response and loss of HBsAg
	Time of Assessment
On-therapy	During therapy
Maintained	Persist throughout the course of treatment
End-of-treatment	At the end of a defined course of therapy
Off-therapy	After discontinuation of therapy
Sustained (SR-6)	6 months after discontinuation of therapy
Sustained (SR-12)	12 months after discontinuation of therapy

HIV and Hepatitis B





Hwang and Cheung NAJMS. 2011;4(1):7-13

http://data.unaids.org/pub/globalreport/2008/2008_globalreport_graphics_presskit_en.pdf

HIV and Hepatitis B Coinfection

- Key antiretrovirals have activity against hepatitis B
  - Lamivudine (resistance mutations emerge after median 18m)
  - Tenofovir use increasing (durable response though breakthroughs may occur)
- Limited screening, does it change management?
  - Earlier ART?
  - Earlier HCC screening?

What About HCC Screening?

- HCC is a terminal diagnosis
- Ultrasounds are available, but do they change management?
- What is the cost to the family?
  - Of the test?
  - Of ineffective treatment for the malignancy?

Clinical Case

- 18 year old Ugandan female, biopsy was performed, pathology showed HCC
- Palliative care team in hospital visited the patient and gave support
- She was discharged home without further treatment

One Step at a Time

Strategies

- Blood bank safety
- Safe injection technologies
- Education to family contacts regarding transmissability of Hep B and Hep C
- Maternal screening for Hep B and birth dose vaccine
  - Monovalent vaccine for household contacts +/- with prescreening
- Targeting tenofovir roll out where supplies are limited to those who are HBV positive

Prevention is Key!

QUESTIONS?