Hepatitis Awareness Month

Identifying and Managing Hepatitis B at the Primary Care Level During COVID-19

Wednesday, May 27, 2020 at 12:00 pm ET

Moderator: Christine Simon, MPH, Public Health Project Manager, NNCC

NATIONAL NURSE-LED CARE CONSORTIUM
a PHMC affiliate

HEPATITIS B FOUNDATION

National Nurse-Led Care Consortium

The **National Nurse-Led Care Consortium (NNCC)** is a nonprofit member-supported organization working to strengthen community health through quality, compassionate, and collaborative nurse-led care.

NNCC provides expertise to support comprehensive, community-based primary care.

- Direct, nurse-led healthcare services
- Policy research and advocacy
- Training and technical assistance support

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Housekeeping Items

Question & Answer

- Click Q&A and type your questions into the open field.
- The Moderator will either send a typed response or answer your questions live at the end of the presentation.

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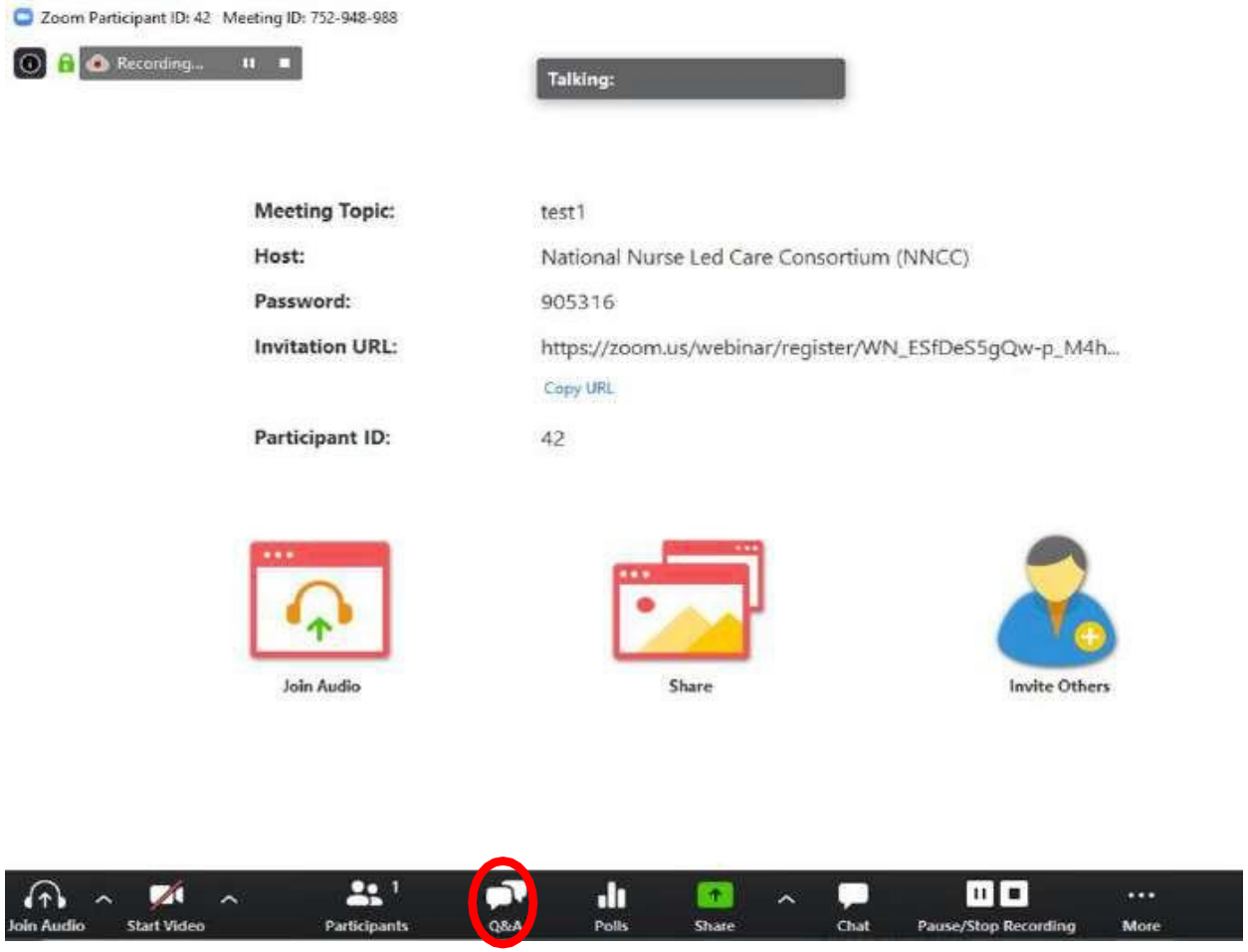


Identifying and Managing Hepatitis B at the Primary Care Level During COVID-19

Wednesday, May 27th, 2020 at 12PM ET

Robert Gish, MD, Medical Director, Hepatitis B Foundation

Catherine Freeland, MPH, Hepatitis B Foundation

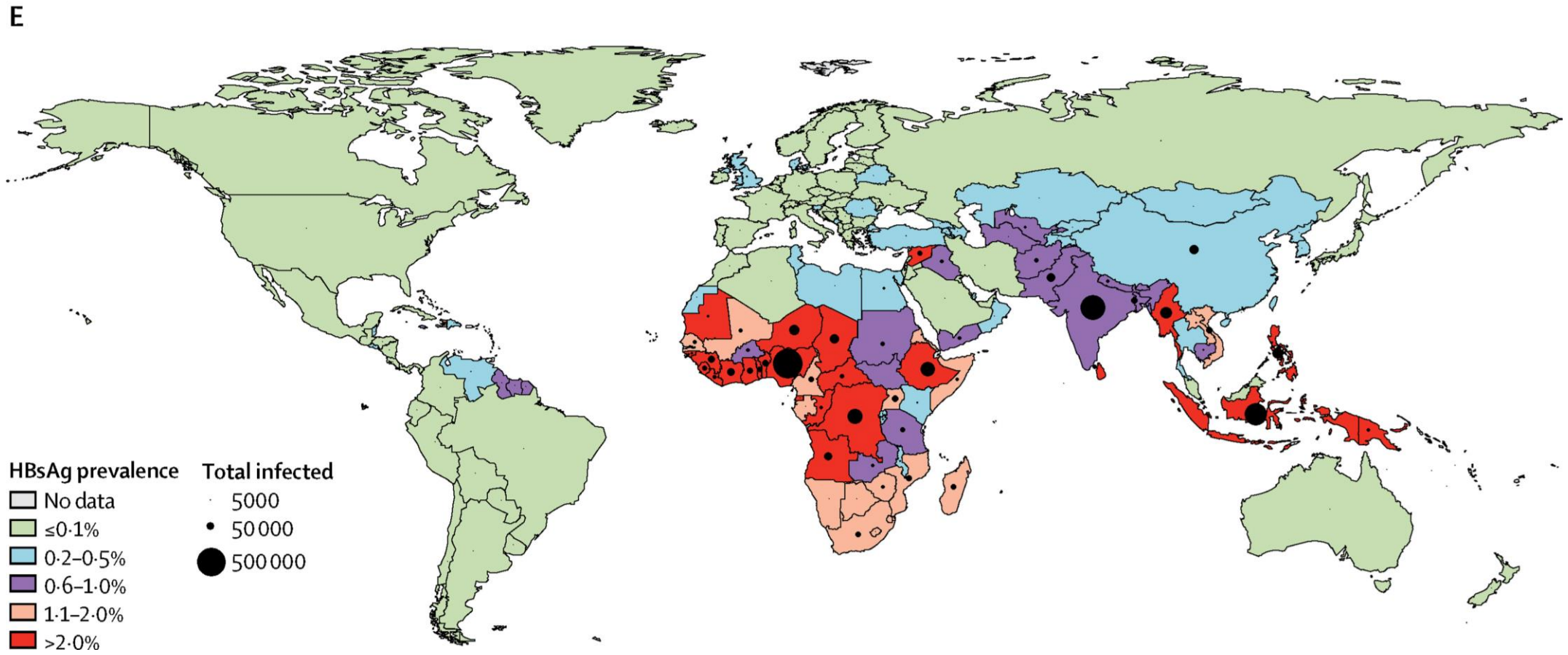
Agenda

- Hepatitis B (HBV) Epidemiology
- HBV serology & testing recommendations for Primary Care Providers
- HBV management for Primary Care Providers (highlighting when to transition to a specialist)
- HBV & COVID-19
- Question and Answer

Objectives

- Describe the epidemiology and virology of hepatitis B in the U.S. and globally, including perinatal hepatitis B
- Summarize the natural history of hepatitis B
- Recommend screening for HBV
- Facts and Fictions of HBV
- Treatment options for HBV

Who is at risk for hepatitis B?
Where do the people affected by HBV live?



The Lancet Gastroenterology & Hepatology 2018 3, 383-403DOI: (10.1016/S2468-1253(18)30056-6)

Table 1 Descriptive characteristics and HBV prevalence of sample population between 2009-2019.

	HBsAg +		HBsAg -		Total		
Regular Doctor							
Yes	67	28.0%	1279	46.1%	1348	44.7%	<.0001
No	167	69.9%	1445	52.1%	1614	53.5%	
Missing	5	2.1%	52	1.9%	57	1.9%	
Age							
≤ 20	1	0.4%	45	1.6%	46	1.5%	0.0001
21 - 30	32	13.4%	257	9.3%	289	9.6%	
31 - 40	59	24.7%	392	14.1%	451	14.9%	
41 - 50	52	21.8%	626	22.6%	678	22.5%	
51 - 60	64	26.8%	714	25.7%	778	25.8%	
61 - 70	22	9.2%	457	16.5%	479	15.9%	
> 70	6	2.5%	261	9.4%	267	8.8%	
Missing	4	1.7%	27	1.0%	31	1.0%	
Region of Birth							
Americas	0	0.00%	166	6.0%	166	6.0%	<.0001
Africa	25	10.5%	282	10.2%	307	11.1%	
European	0	0.0%	4	0.1%	4	0.1%	
Eastern Mediterranean	0	0.0%	6	0.2%	6	0.2%	
South East Asia	7	2.9%	296	10.7%	305	11.0%	
Western Pacific	204	85.4%	1981	71.4%	2186	78.7%	
Missing	3	1.3%	42	1.5%	45	1.6%	

Data provided not yet published

Hepatitis B Infection among immigrant populations

- Migration accounts for 95% of new cases in US
- 90% of foreign-born persons with HBV migrated from regions of intermediate (2%-7%) to high (≥8%) endemicity

Top countries of origin of foreign-born persons with HBV in the US (2009):

- China
- Vietnam
- Philippines
- Dominican Republic
- Mexico

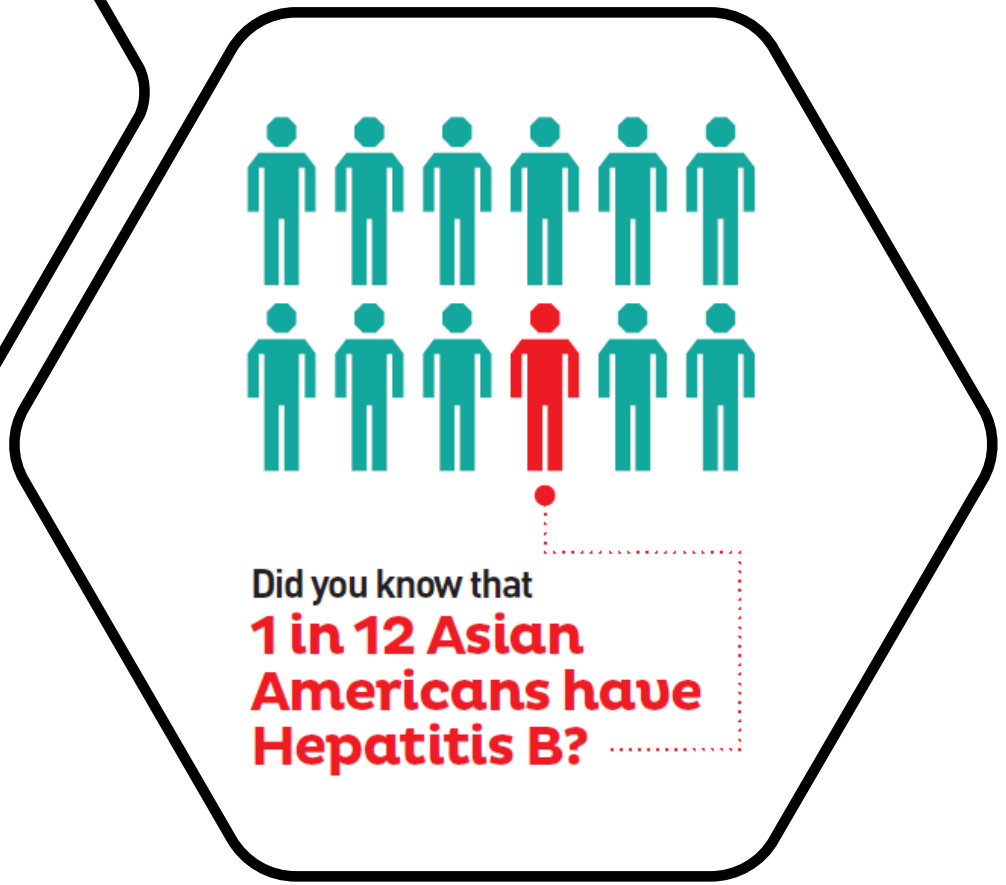
HBV prevalence rate among foreign-born persons by region (2012):

- Africa (10.3%)
- Asia (7.27%)
- Oceania (4.78%)
- Caribbean (4.52%)
- All (3.45%)

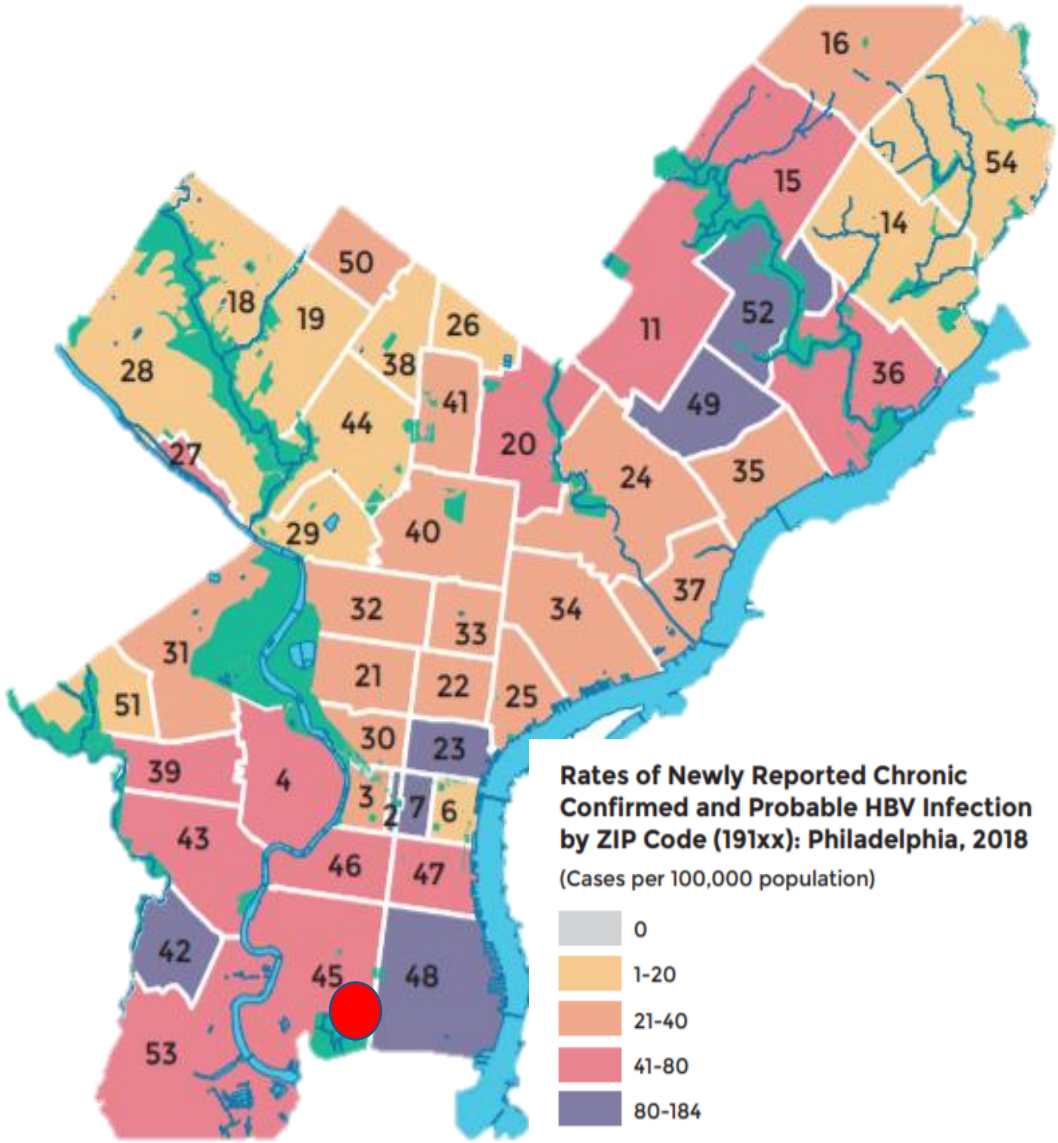
Source: Kowdley KV, et al. Hepatology. 2012;56:422-433.
Mitchell T, et al. PLoS ONE. 2011;6(12):e27717.

HBV-Related Health Disparities

- Asian Americans & Pacific Islanders carry 50% of chronic HBV burden in the US
- 5% - 15% infection rates have been found in African-born community-based studies in the U.S.
- HBV doubles the rate of liver cancer
- AAPI: Six times the rate of HBV-related mortality



Chronic HBV in Philadelphia



- **30%** of persons living with HBV are currently out of care.
- Areas of the city with populations of persons who have immigrated from Africa, Asia, and Eastern Europe have

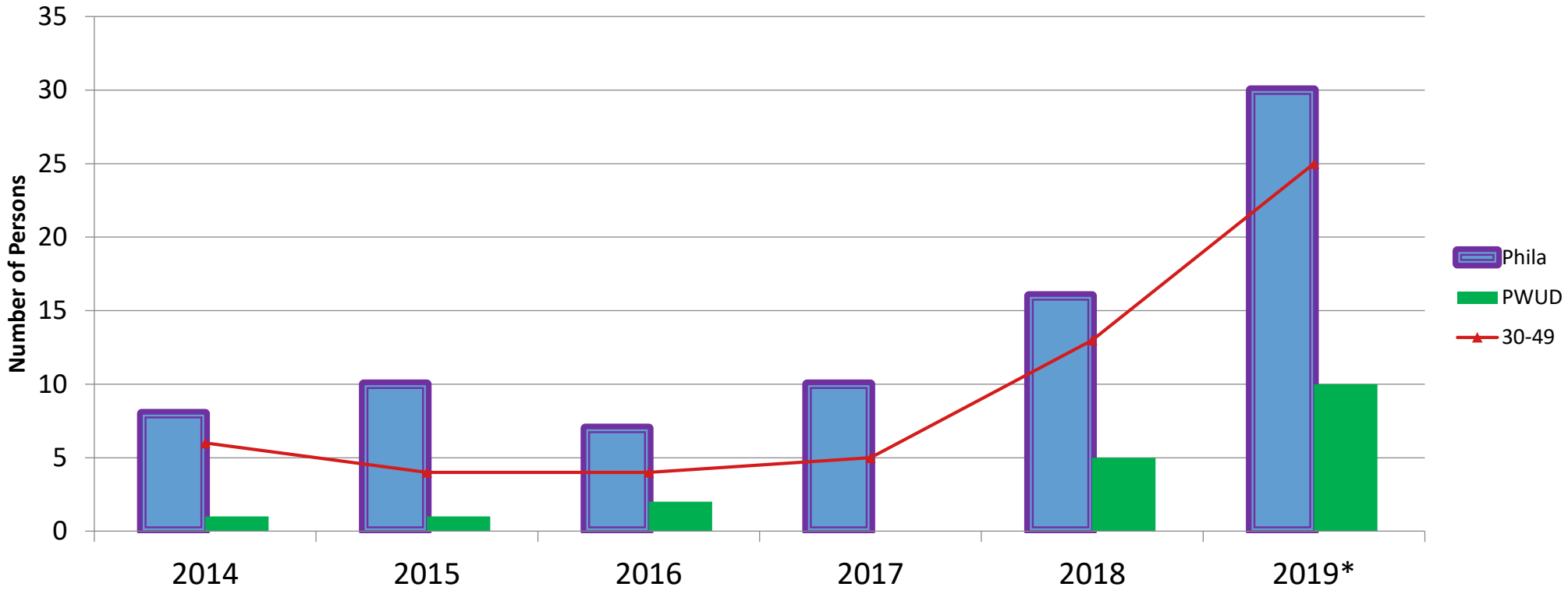
Data provided by the Philadelphia Department of Public Health

Hepatitis B in Philadelphia

Surveillance-based HBV Data, Philadelphia						
		2014	2015	2016	2017	2018
Acute Cases		8	8	7	10	12
PHBPP mother-infant pairs		164	155	174	141	144
New Chronic Cases						
Total		884	789	809	730	782
Sex	Male	480	471	470	432	459
	Female	401	317	336	295	316

Data provided by the Philadelphia Department of Public Health

Acute HBV in Philadelphia



Data provided by the Philadelphia Department of Public Health

Department of Public Health
CITY OF PHILADELPHIA

Philadelphia Department of Public Health

Division of Disease Control

THOMAS A. FARLEY, MD, MPH
Health Commissioner

CAROLINE JOHNSON, MD
Deputy Health Commissioner

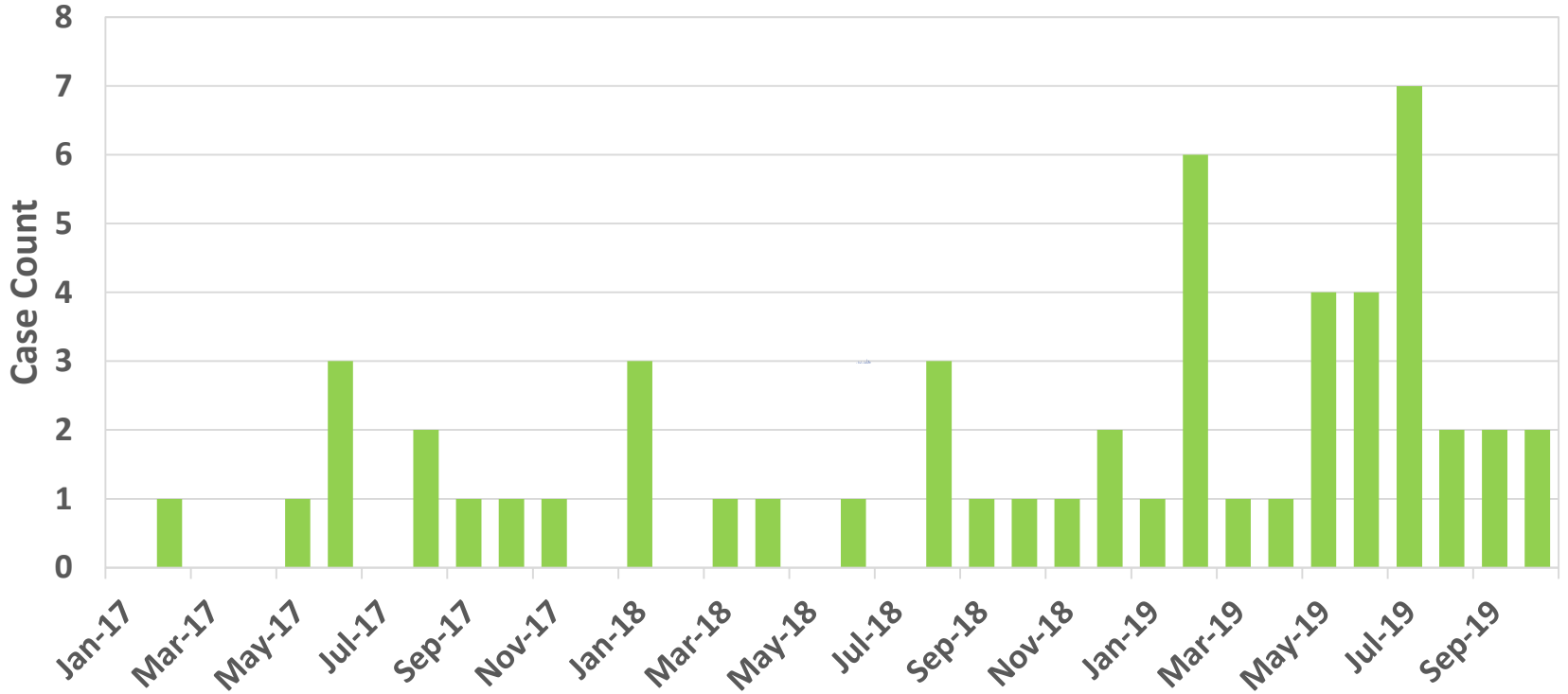
STEVEN ALLES, MD, MS
Director, Division of Disease Control

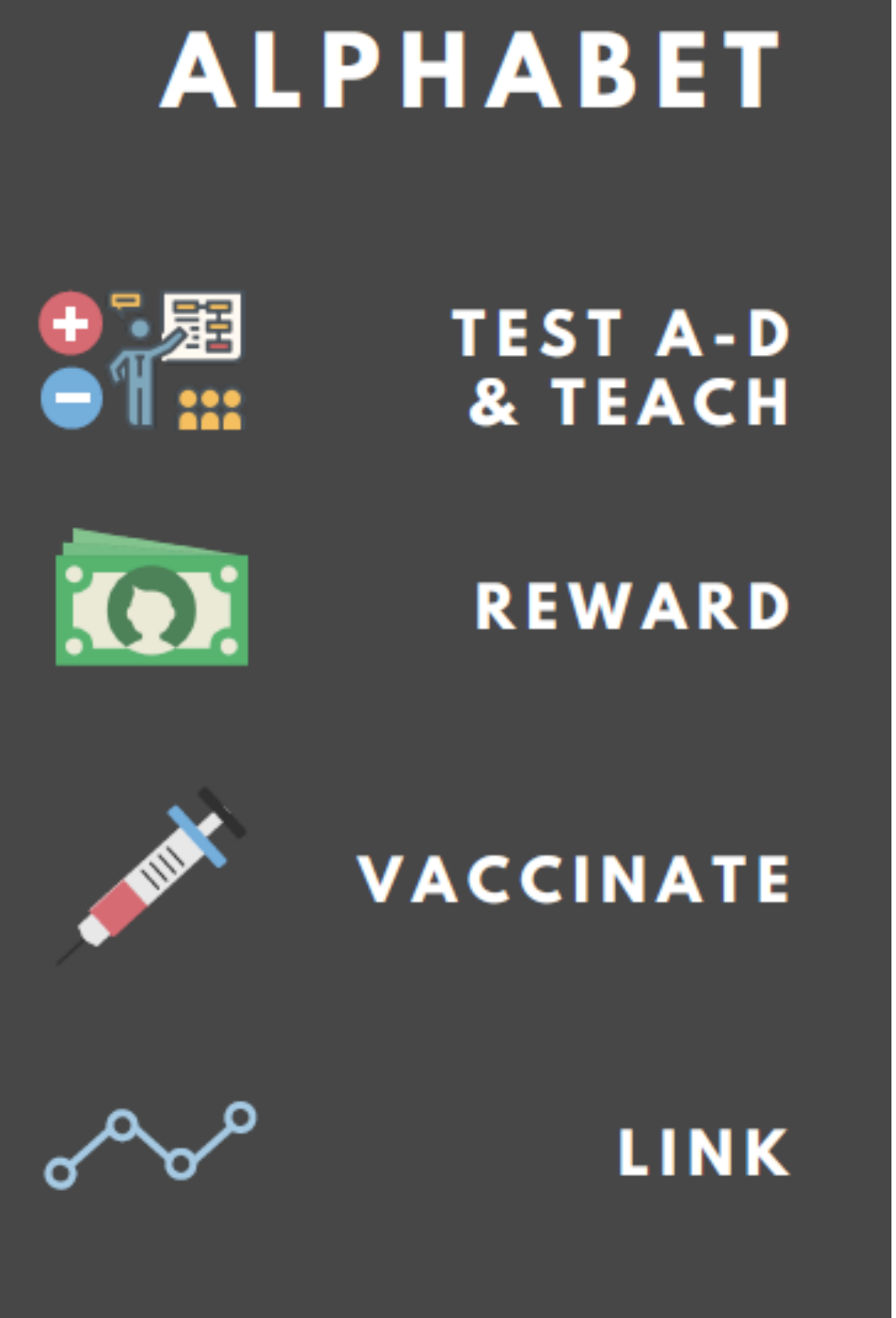
Health Advisory

Acute Hepatitis B Increases in Philadelphia

December 13, 2019

175% increase in confirmed acute hepatitis B cases from 2017-2019; especially among PWUD, and those living homeless





Viral Hepatitis Serology Study at Prevention Point

HEP partnership with PPP & Hep B Foundation

- Started January 9th, 2018
- Enrolled 438 PPP Clients 18-39 years old
  - Questionnaire
  - Blood Draw
- Test for Infection and Immunity to Hep A, HepB,

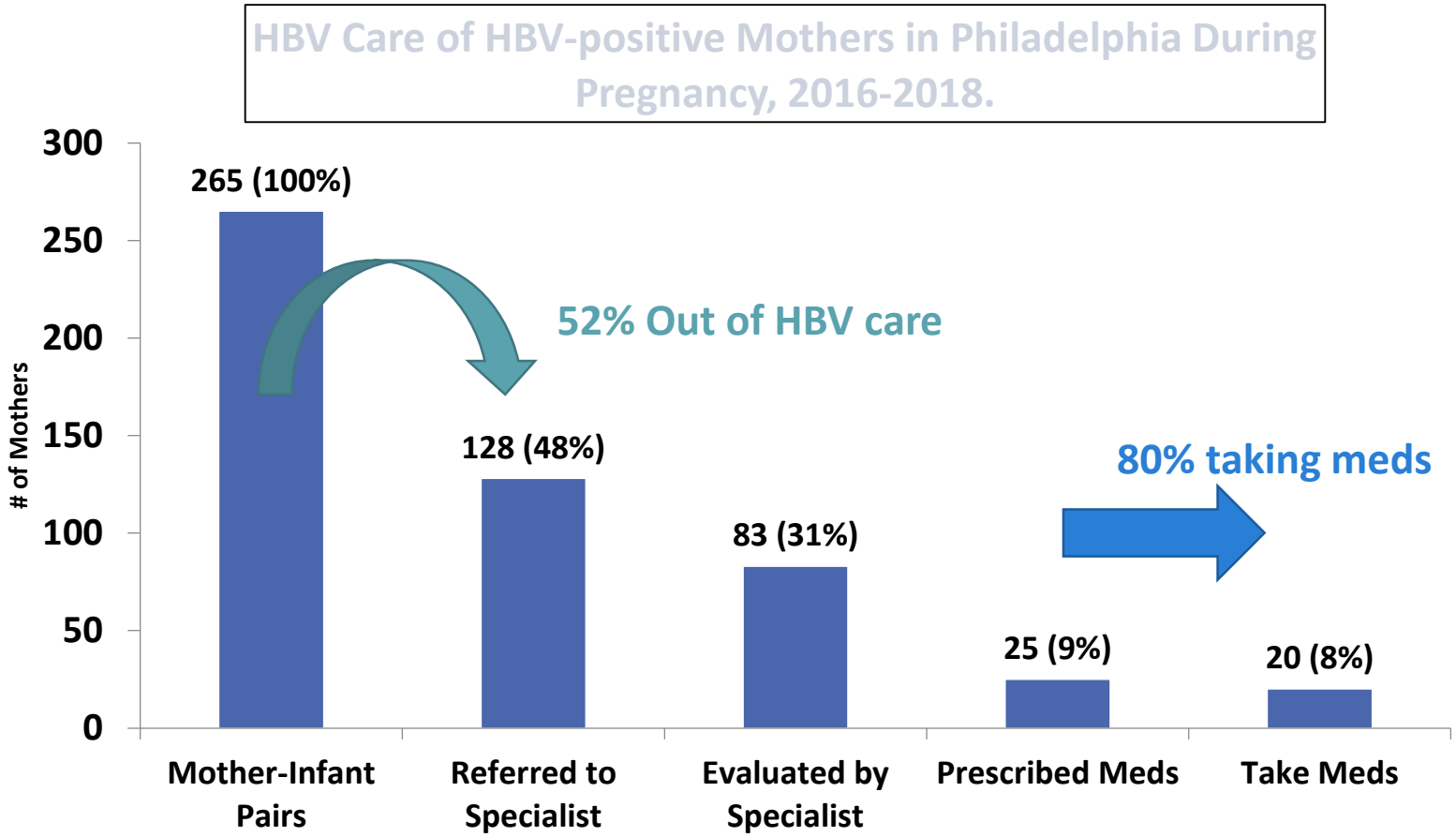
  HepC, and HepD
- Link clients with infections to care and provide HepA and HepB vaccine to non-immune
- Measure rates of immunity and viral hepatitis infection among PWID in Philadelphia to inform practice

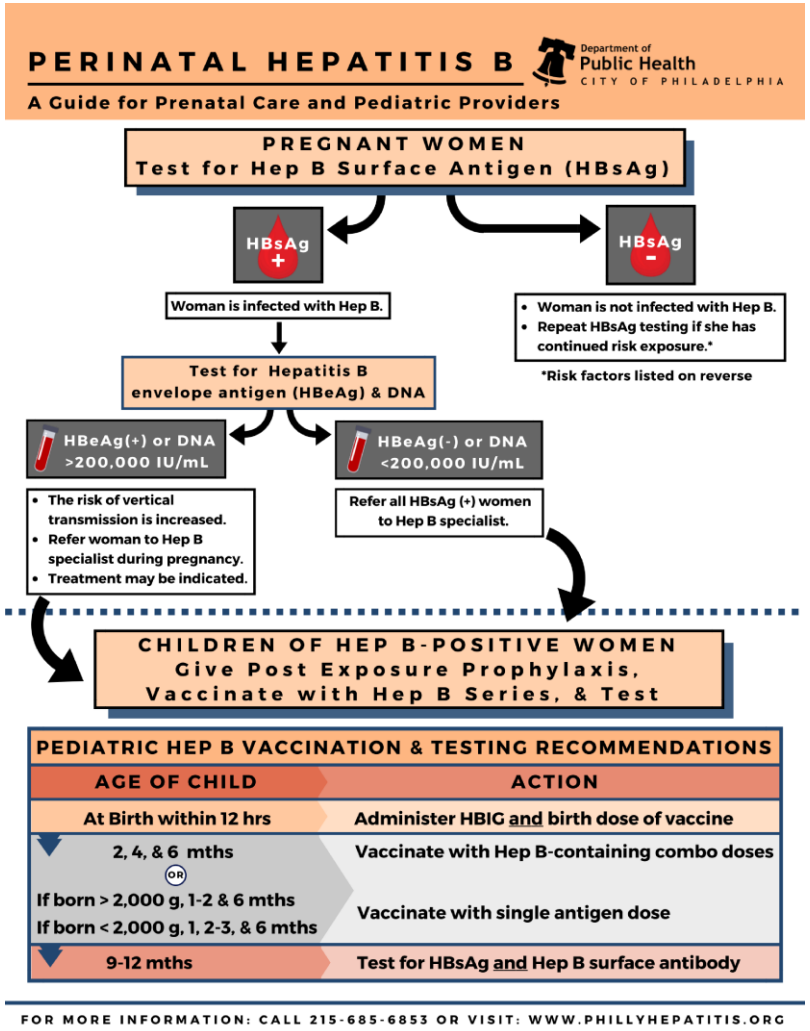
Prevalence & Immunity of HEP A,B,C,D

Immunity Status	N=384	%
Hep A		
Susceptible	186	48.4
Immune - vaccine or past exposure	198	51.6
Hep B		
Susceptible	148	40.9
Immune - vaccine	153	42.3
Immune - past exposure	61	16.9
Hep A & B		
Susceptible	93	25.8

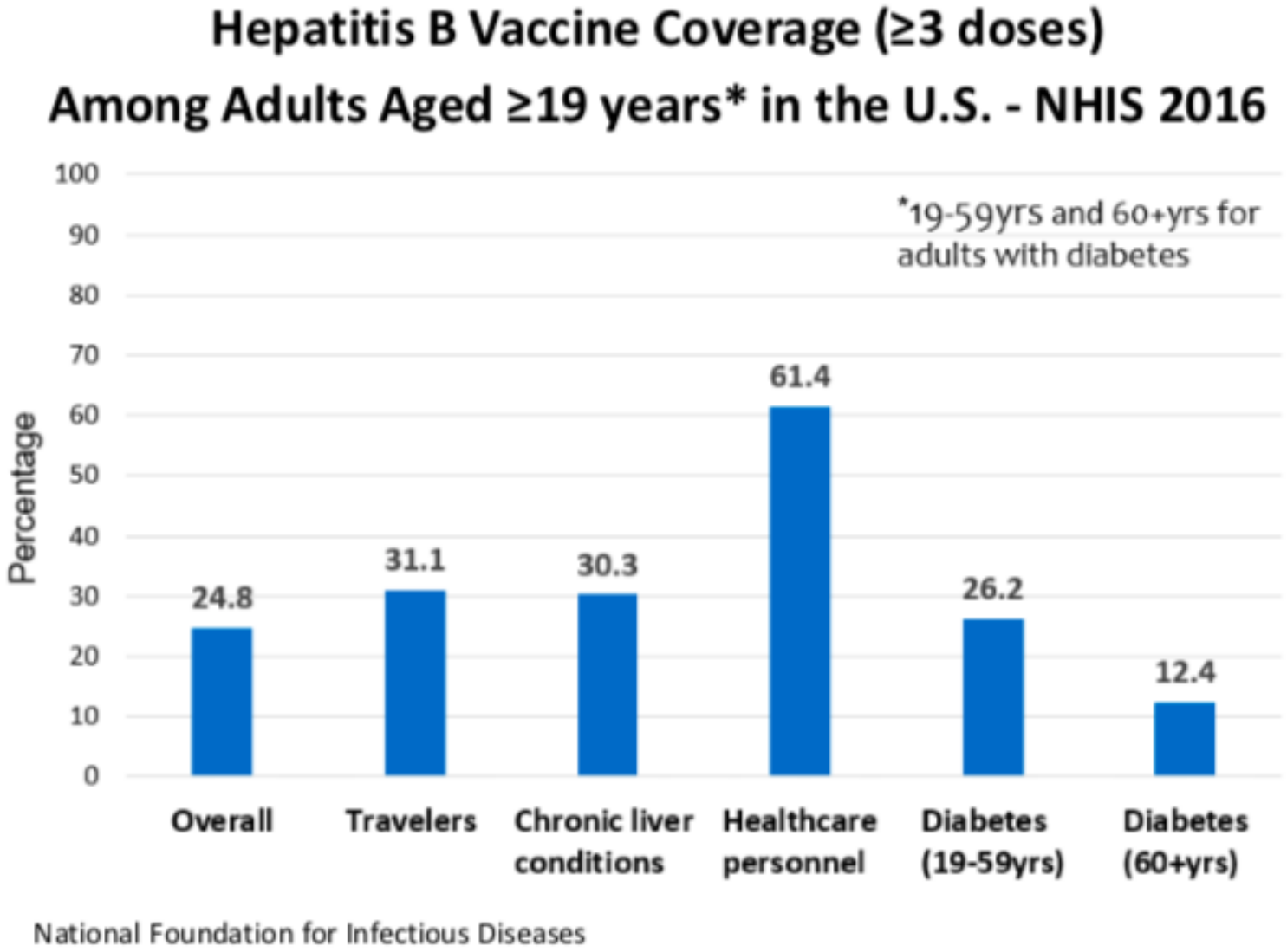
Serological Status	N=384	%
Hep A		
Acute Infection	0	0.0
IgM Positive – Not a case*	1	0.3
Hep B		
Current infection	7	1.8
Past/cleared infection	77	20.3
No infection	295	77.8
Hep C		
Current infection	160	42.3
Past/cleared infection	46	12.2
Past or Current infection - status unknown[†]	19	5.0
No infection	153	40.5
Hep D		
Past/present infection	4	1.1
No infection	375	98.9

Perinatal Hepatitis B Program





Adult Vaccination Coverage



Hepatitis B: Update 2020

Robert Gish MD, FAASLD, AGAF, FAST
Robert G Gish Consultants LLC – Principal
Hepatitis B Foundation - Medical Director
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University of Nevada Las Vegas
University of Nevada Reno
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- Please see www.robertgish.com
- Speaker’s Bureau - Gilead

HBV Disease Progression

~ 2 people per minute will die from complications associated with HBV

Chronic Infection

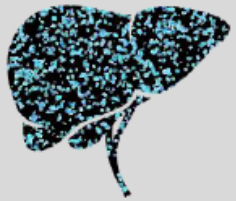
>250 million chronically infected worldwide

8% diagnosed

<1% receive treatment

1%-3% of those receiving treatment with current options achieve functional cure

Cirrhosis/HCC



20%-30%

Surgery, chemotherapy, and liver transplant

Death

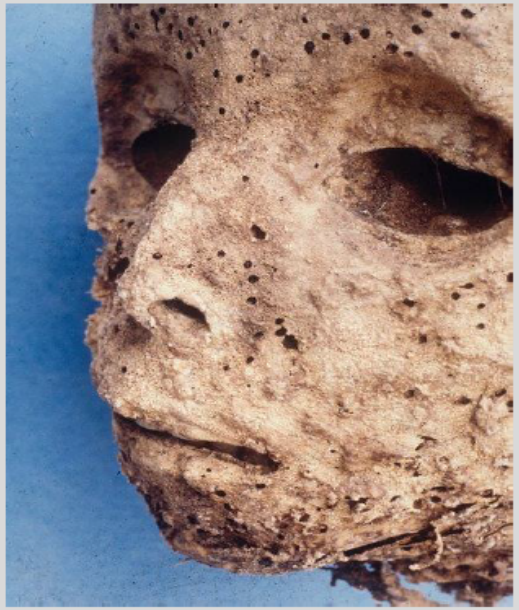
~1 million people/year

2 people/minute

How Old is HBV?

The Paradox of HBV Evolution As Revealed From a 16th Century Mummy

Zoe Patterson Ross, Jennifer Klunk, Gino Fornaciari, Valentina Giuffra, Sebastian Duchêne, Ana T. Duggan, Debi Poinar, Mark W. Douglas, John-Sebastian Eden, Edward C. Holmes , Hendrik N. Poinar

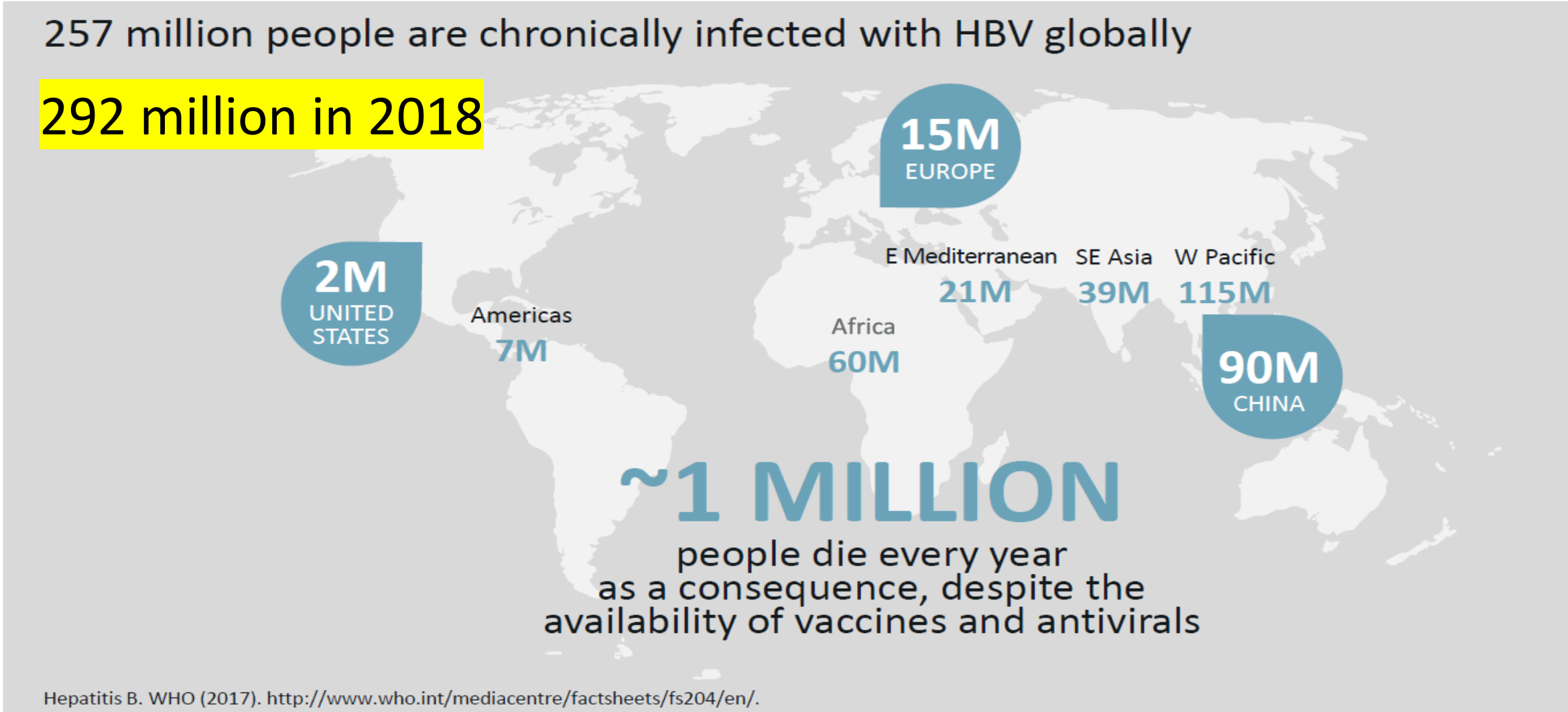


- 16th century Italian mummy
- Previously thought to have smallpox
- No variola DNA identified, but HBV DNA identified
- Phylogenetically closely related to present-day genotype D
- HBV genotypes diversified long before the 1500s
- HBV evolution evades molecular clock to date its origin

HBV = hepatitis B virus.

PLOS Pathogens. http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006750. January 4, 2018.

Tremendous Medical Need



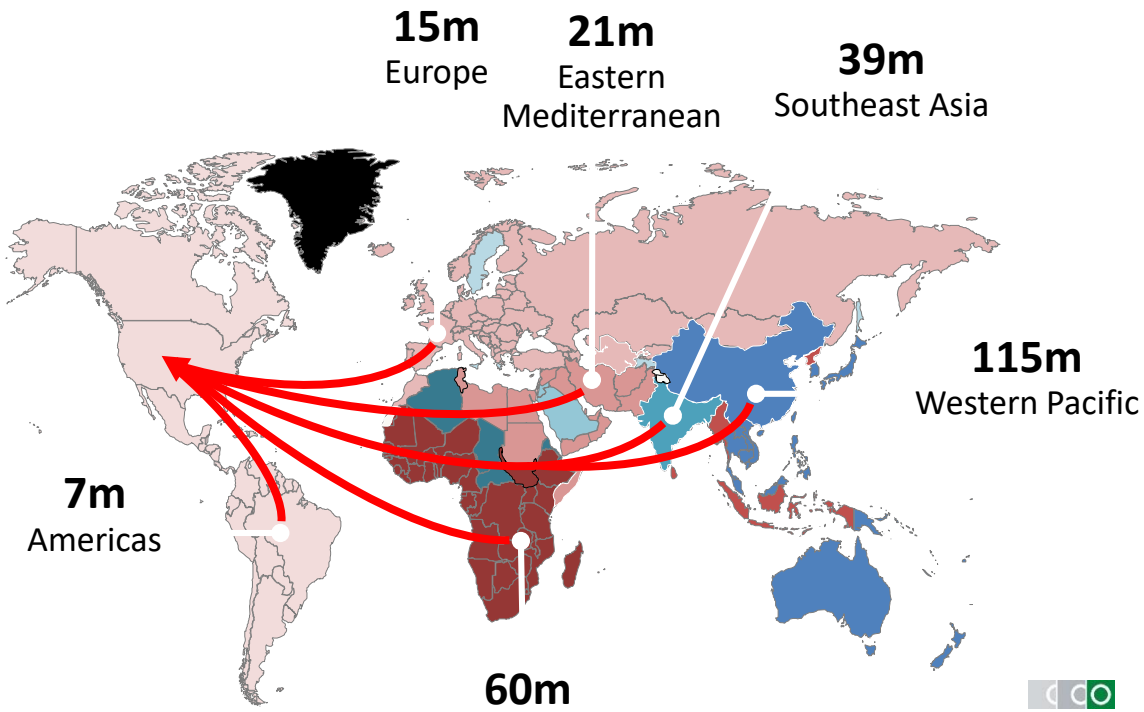
Hepatitis B. WHO (2017). http://www.who.int/mediacentre/factsheets/fs204/en/.

Estimated Prevalence of CHB

US Prevalence of CHB in Foreign-Born Persons in 2009[1]

Birth Country	Total (M)	Midrange CHB Prevalence (%)
All regions	38.4	3.5
Asia	10.6	7.3
Central America	14.4	< 1.0
Caribbean	3.4	4.5
South America	2.6	1.3
North America	0.8	< 1.0
Oceania	0.19	4.8
Africa	1.5	10.3
Europe	4.9	2.0

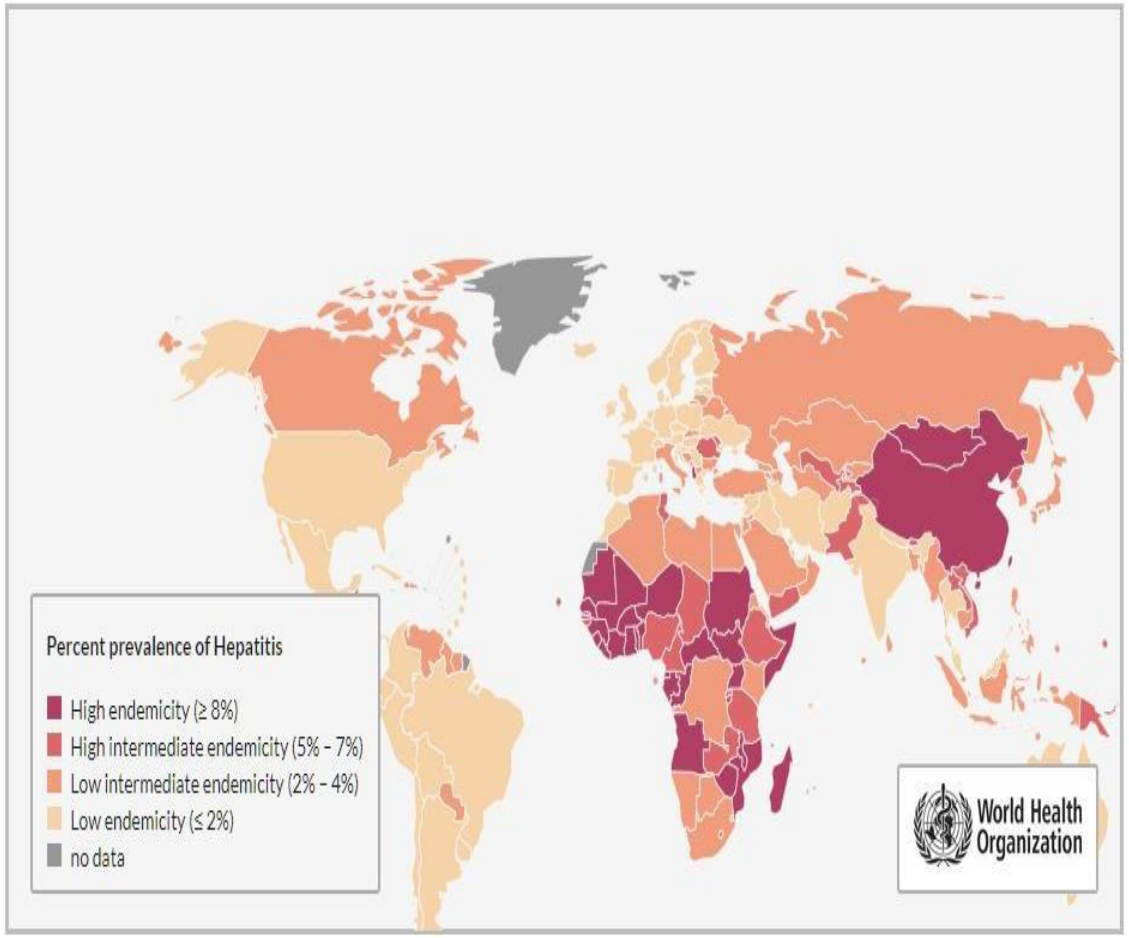
Global Prevalence of CHB in 2015: >257 Million[2]



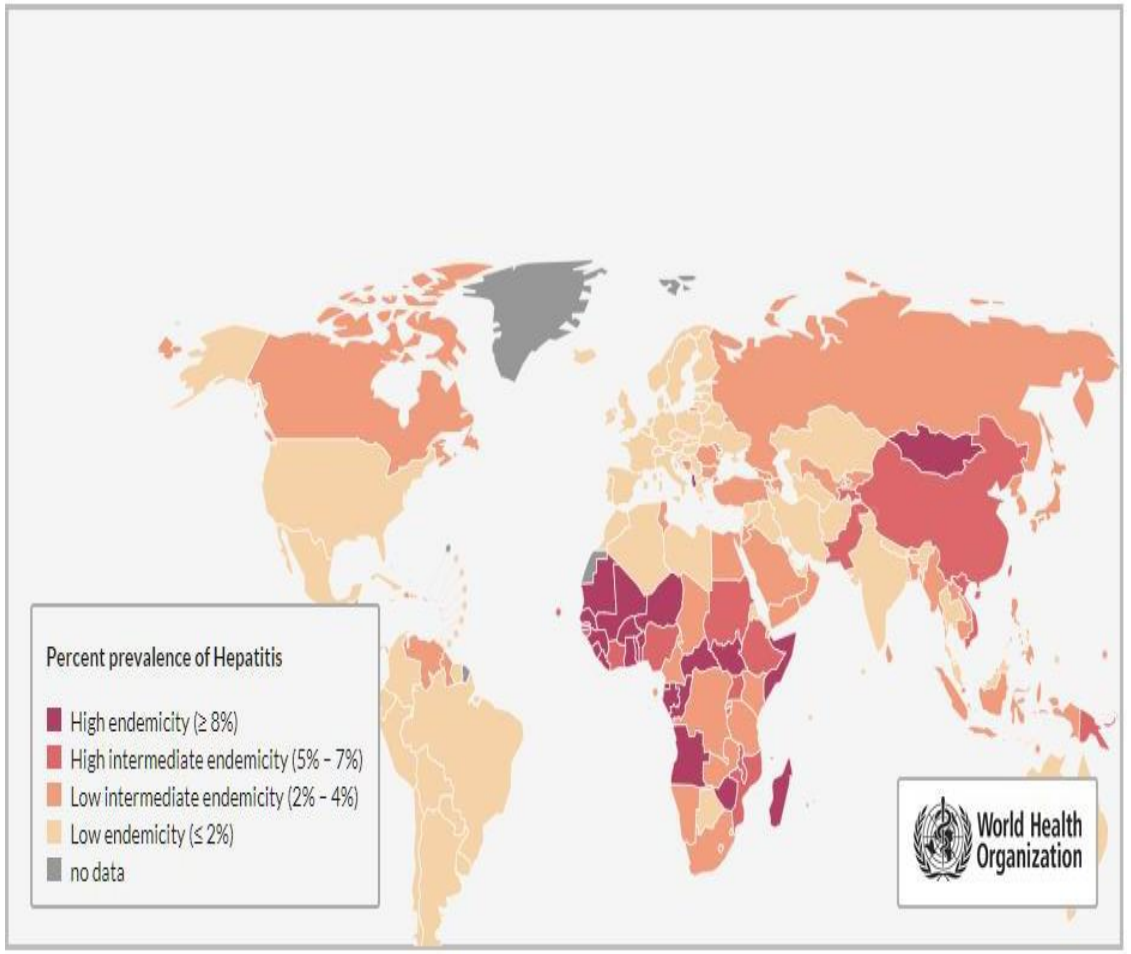
1. Kowdley. Hepatology. 2012;56:422. 2. WHO. Global hepatitis report, 2017.

Slide credit: clinicaloptions.com

HBsAg prevalence estimates:
All ages: Vaccine is making a difference



HBsAg all ages pre vaccination 1990



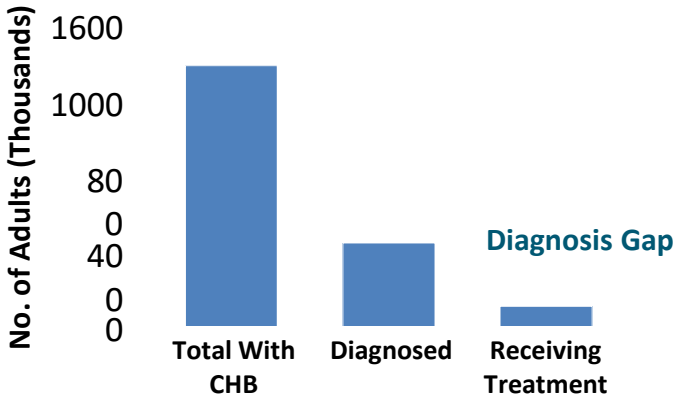
HBsAg all ages 2015 estimates

Prevalence of CHB in the United States and linkage to care

Including foreign-born persons, **850,000 to 2.2 million people in the US** are living with CHB,[1] including **400,000 to 800,000 Asians**[1,2]

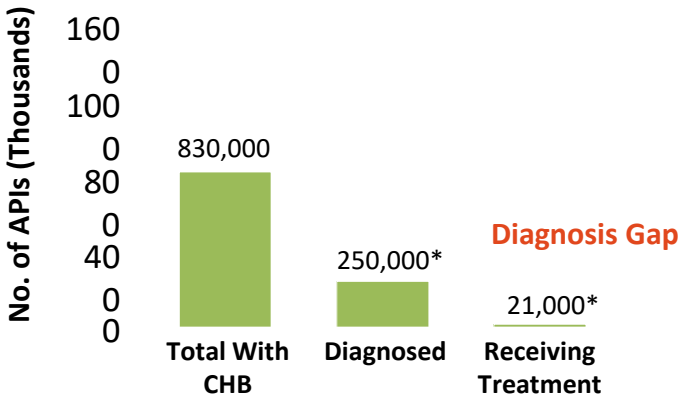
2013-2016 estimated CHB prevalence in **US** was 0.7%[3]

Diagnosis and Treatment Gaps in US Population[3]



2007 CHB prevalence among foreign-born **APIs in US** was 8.9%[4]

Diagnosis and Treatment Gaps in US API Population[4,5]



*Estimates established by applying percentage of persons with CHB diagnosed and treated in total population to number of APIs with CHB.

1. Harris. MMWR. 2018;67:541.
2. Kowdley. Hepatology. 2012;56:422.
3. Zhou. Clin Gastroenterol Hepatol. 2019. Epub.
4. Cohen. J Viral Hepat. 2008;15:12. 5. Cohen. J Viral Hepat. 2011;18:377.

Prevalence of Chronic Hepatitis B Infection in the U.S.

Estimated prevalence of 1.59 million persons (range 1.25-2.49 million)

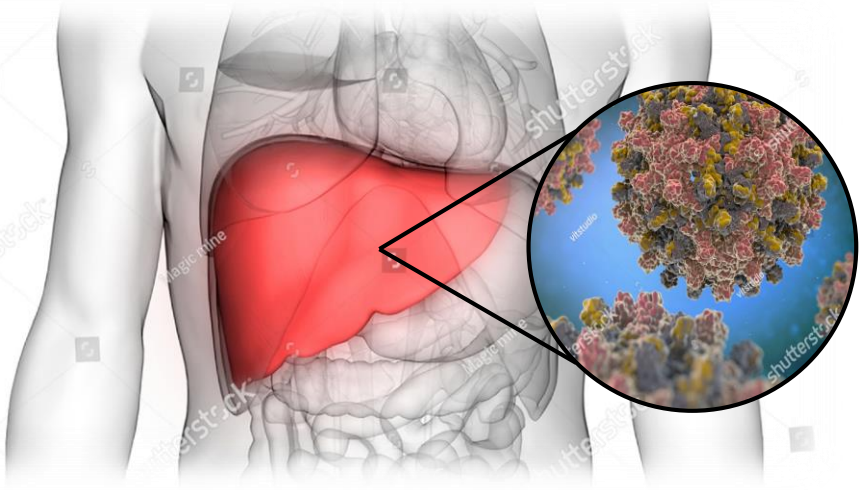
Individuals at-risk for HBV are those who are unvaccinated, fall into high-risk groups or are foreign-born and immigrating from HBV endemic regions (e.g. Asia, Africa),

Veterans
0.3[1] – 0.84%[2]

Healthcare Professionals
0.1-8.1%[3]

Prisoners
0.9-11.4%[4]

Homeless People
0.4[5]-1.17%[6]



Men Who Have Sex with Men
Prevalence unknown

People Who Inject Drugs
11.8%[7]

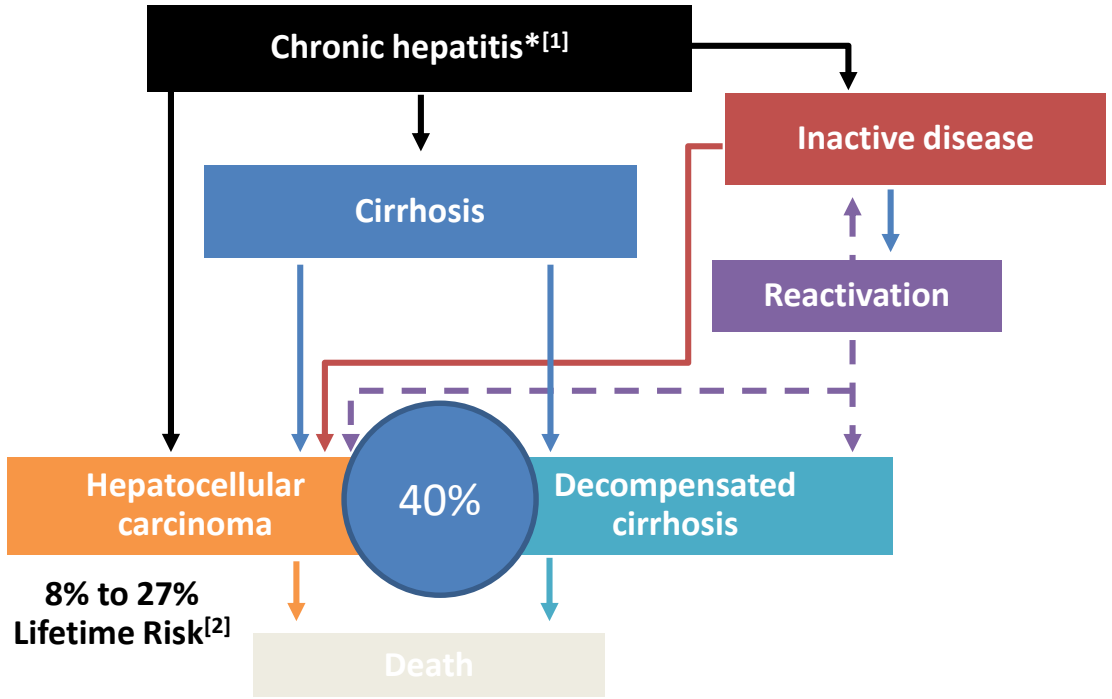
Patients with HIV Coinfection
0.7-5.8%[8-12]

Patients HCV Coinfection
3.0-8.4%[13-15]

Newborns Born to HBV-Infected Mothers
3.84%[16]

AJG 2020 Lim in press

Hepatitis B Disease Progression and Impact



*Failure to clear HBsAg 6 mos after acute infection.

Up to 40% of persons with CHB develop significant clinical consequences, including cirrhosis, liver failure, and HCC[3]

25% of persons with CHB will die prematurely from complications[4]

1. The elimination of hepatitis B. In: Buckley. Eliminating the public health problem of hepatitis B and C in the United States: Phase One Report. 2016.

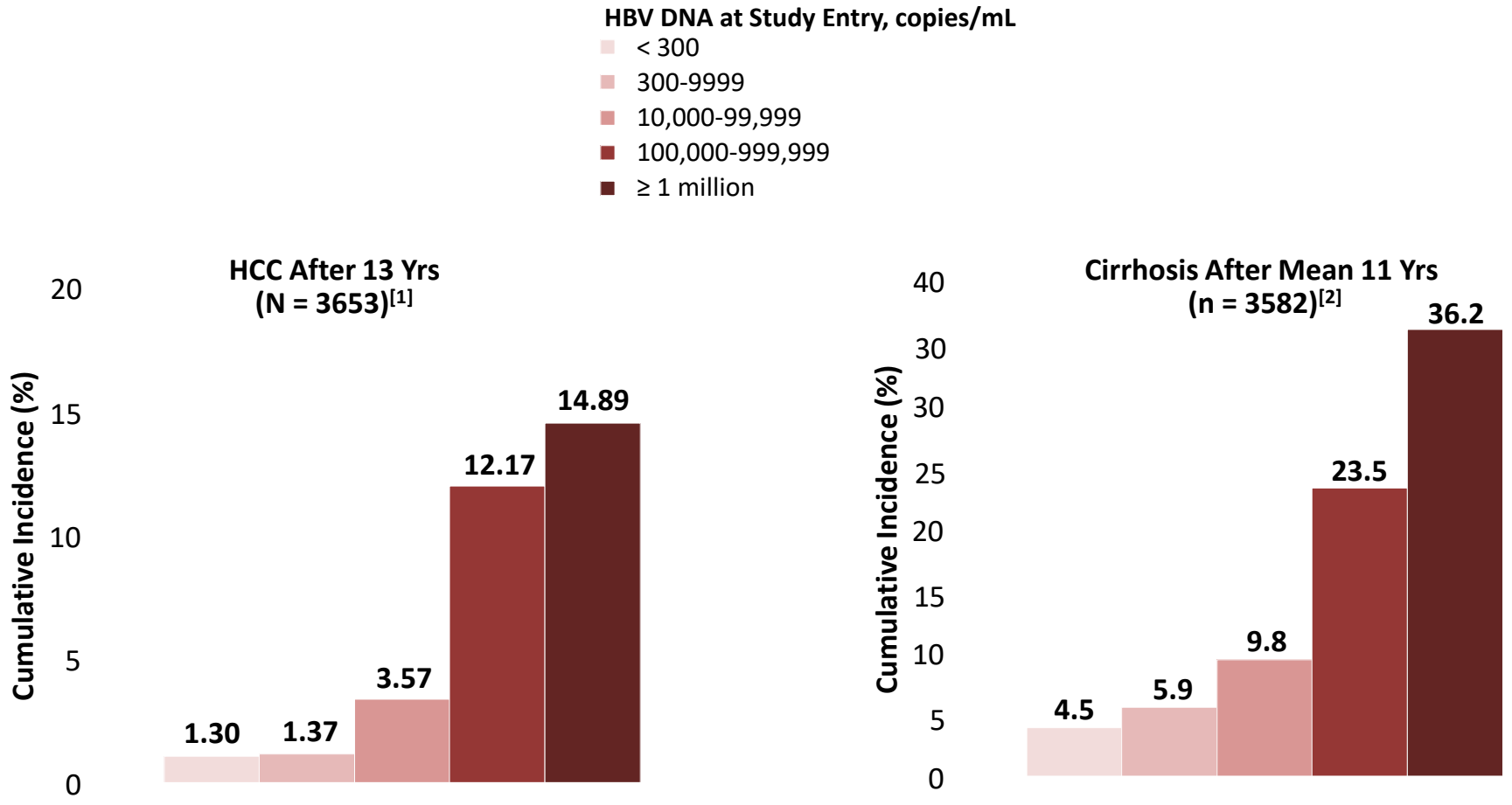
2. Huang. JCO. 2011;29:3643.

3. Lok. NEJM. 2002;346:1682.

4. Harris. MMWR. 2018;67:541.

Slide credit: clinicaloptions.com

REVEAL-HBV: HBV DNA Levels and Long-term Outcomes



1. Chen. JAMA. 2006;295:65.
2. 2. Iloeje. Gastroenterology. 2006;130:678.

Slide credit: clinicaloptions.com

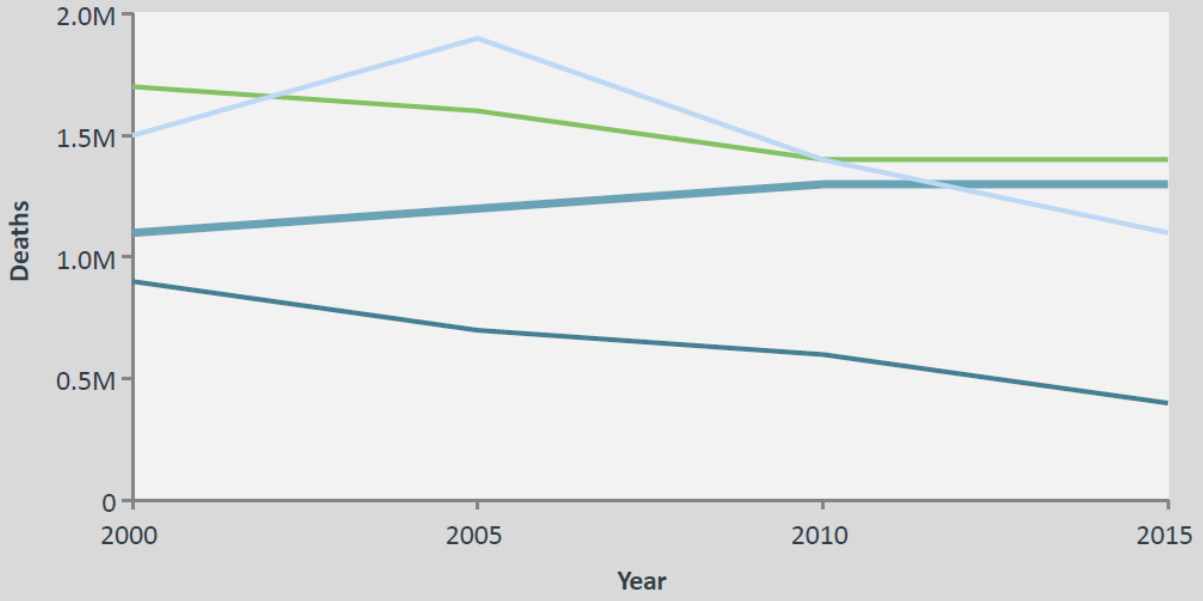
qHBsAg Levels and Risk for HCC

HBsAg Level, IU/mL	Relative Risk	95% CI
Tseng et al[1]		
< 10	1.0	
10-99	1.1	0.3-4.2
100-999	2.3	0.7-7.3
1000-9999	3.2	1.0-10.0
≥ 10,000	2.9	0.9-9.5
Lee et al[2]		
< 100	1.0	
100-999	3.2	1.7-6.1
≥ 1000	5.4	3.0-9.9

1. Tseng. Gastroenterology. 2012;142:1140.
2. 2. Lee. Hepatology. 2013;58:546.

HBV Remains a Serious Disease

Mortality is increasing in hepatitis A, B, E, and C

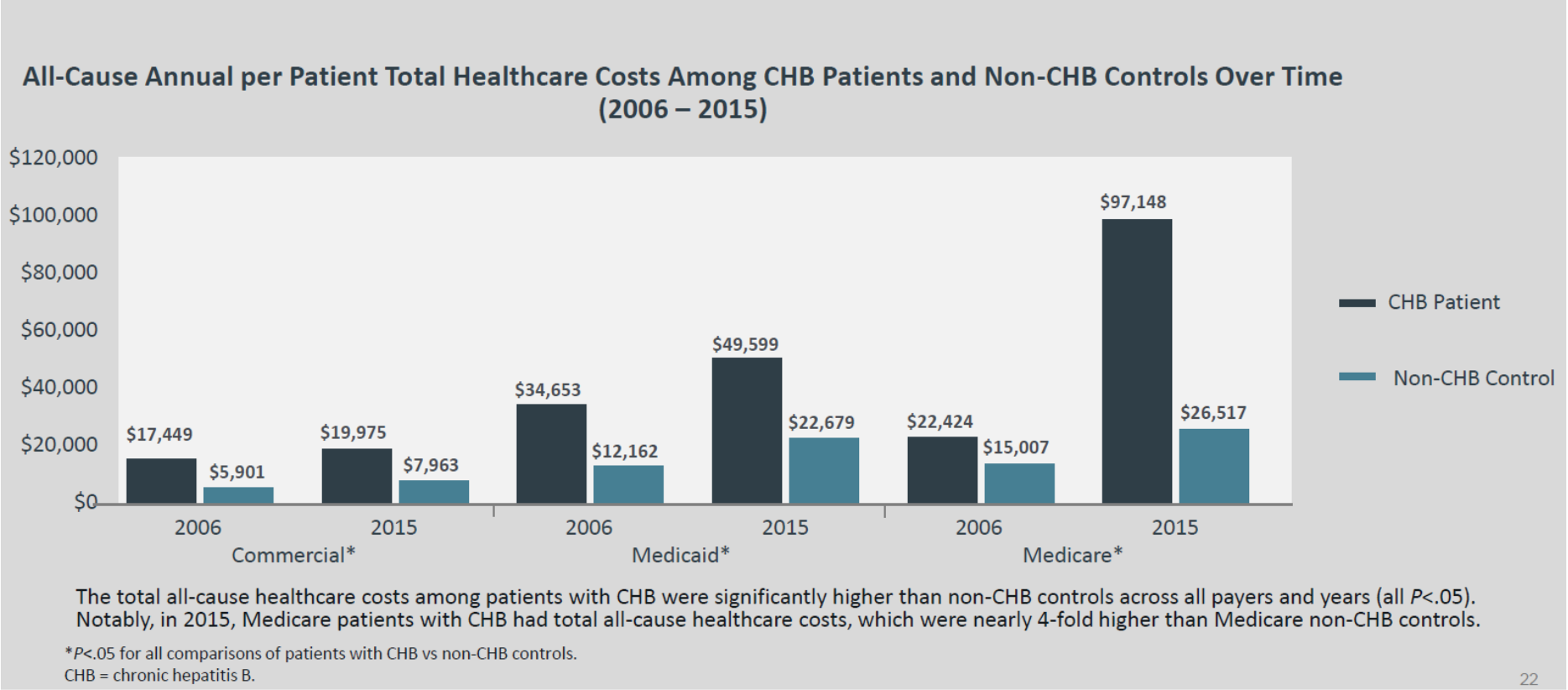


- **1.34 million deaths in 2015**
- 96% of hepatitis deaths are from HBV and HCV (cirrhosis and HCC)

Hepatitis
Tuberculosis
HIV
Malaria

HCC = hepatocellular carcinoma.
Hepatitis B. WHO (Center for Disease Analysis).

Significant Cost of HBV Infection



	2020 Goal	2014 Baseline	2016 Result	2017 Result (2017 Target*)	Status
Hepatitis A					
Increase the percentage of children aged 19–35 months who receive ≥2 doses of hepatitis A vaccine	85.0%	57.5%	60.6%	59.7% (71.3%)	✗
Reduce the rate† of reported hepatitis A virus infections	0.30	0.39	0.62	1.03 (0.35)	✗
Hepatitis B					
Increase the percentage of infants who receive hepatitis B vaccine within 3 days of birth	85.0%	72.4%	71.1%	73.6% (78.7%)	→
Reduce the rate† of reported acute hepatitis B virus infections among persons aged ≥19 years	0.50	1.16	1.31	1.38 (0.83)	✗
Reduce the rate† of hepatitis B-related deaths	0.48	0.50	0.45	0.46 (0.49)	✓
Hepatitis C					
Reduce the rate† of reported acute hepatitis C virus infections	0.25	0.73	0.98	1.04 (0.49)	✗
Reduce the rate† of hepatitis C-related deaths	4.17	5.01	4.42	4.13 (4.59)	✓

* Target for 2017 assumes a constant (linear) rate of change from the observed baseline (2014) to the 2020 goal
† Per 100,000 U.S. population

✓ Met or exceeded current annual

→ Moving **toward** annual target, but annual target was not fully met

✗ Annual target was not met and was not changed or moved **away** from annual target

HBV Tests Part I

- +HBsAg = infection (Test all patients for HDV)
- +Anti-HBc = exposure = cccDNA = persistence
  - Eval for Occult HBV if HBsAg (-)
  - Reactivation risk
  - No vaccine boosting
- +Anti-HBs = immunity, if anti-HBc is negative
- HBV is incurable
- There is no “natural immunity”

Evaluating the HBsAg+ patient: HBV Tests Part II

- For all HBsAg + patients we need these blood tests
  - HBeAg
  - Anti-HBe
  - HDV antibody total (not IgM) (IF total +)>> qHDV RNA reflex
  - HCV antibody
  - qHBsAg
- US doppler with spleen and PV size
- HBV DNA quant
- HAV antibody total
- HIV antibody
- AFP/ DCP AFP-L3% and GALAD score
- Fibroscan CAM
- NASH assessment

Evaluating the HBsAg + Patient Part III

- ALT/AST and calc ratio
- Family History of HCC and cirrhosis
- Liver biopsy only if mixed picture of other diseases
- Fibrosure/test serum makers of fibrosis
- Alcohol history and current use
- Renal function
- Bone DEXA
- APRI
- Fib4
- Pregnancy if appropriate
- Family testing for HBsAg, anti-HBs, and anti-HBc

Interpretation HBV serologic test results for HBV infection and Further Actions

	Profile 1	Profile 2	Profile 3	Profile 4	Profile 5
1. HBsAg	Negative	Negative	Positive	Negative	Negative
2. Anti-HBc	Negative	Negative	Positive	Positive	Positive
3. Anti HBs	Negative	Positive	Negative	Positive	Negative
Significance	1. No chronic infection; not a hepatitis B carrier.	1. No chronic infection; not a hepatitis B carrier.	1. Has acute or flare (if HBc IgM+) or 99% chronic hepatitis B infection.	1. No hep B infection in the blood if HBV DNA negative	1. Subclinical infection at the moment if HBV DNA + OBI
	2. Never been infected with hepatitis B virus.	2. Not infected with hep B virus.	2. Is infected with hep B virus. Has cccDNA in the liver	2. Has been infected with hep B virus.Has cccDNA in the liver	2. Has been infected with hep B virus. Has cccDNA in the liver
	3. No immunity (no protection) against hep B.	3. Has immunity due to vaccination.	3. No immunity or protection against hep B.	3. Has cleared the blood of HBV infection (when combined with negative HBsAg) And has immune control	3. OBI: subclinical infection HBV DNA + and has risk of reactivation.
Action	--	--	See Primary care provider for further tests. HBV DNA quant.	Watch for reactivation if becomes immune suppressed	Watch for risks of reactivation if patient become immune suppressed No vaccination boosting
	Provide vaccination	No vaccination needed	No vaccination needed	No vaccination needed	No vaccination needed

Natural History of CHB: New 5 phase model

Chronic infection High Replicative, Low Inflammatory

- High HBV DNA
- Trained immunity*
- Normal or low ALT
- HBeAg(+)
- High serum levels of HBeAg & HBsAg
- Mild or no necroinflammation
- No or slow fibrosis progression
- Decreased IL-10, IL-6, IL-8 & TNF-α
- No HBV DNA mutations

Chronic Hepatitis Immune Clearance

- High changing to low or undetectable HBV DNA
- High decreasing to normal ALT
- Acute or intermittent hepatitis
- Declining HBeAg & HBsAg
- Eventual loss of HBeAg
- High changing to minimal necroinflammation
- Emergence of core and precore mutations

Chronic Hepatitis HBeAg(-) Chronic

- Moderate to high HBV DNA
- High but fluctuating ALT
- Low HBsAg levels
- Persistent hepatitis
- Necroinflammation
- Progressive liver disease
- Immune clearance attempts ineffective

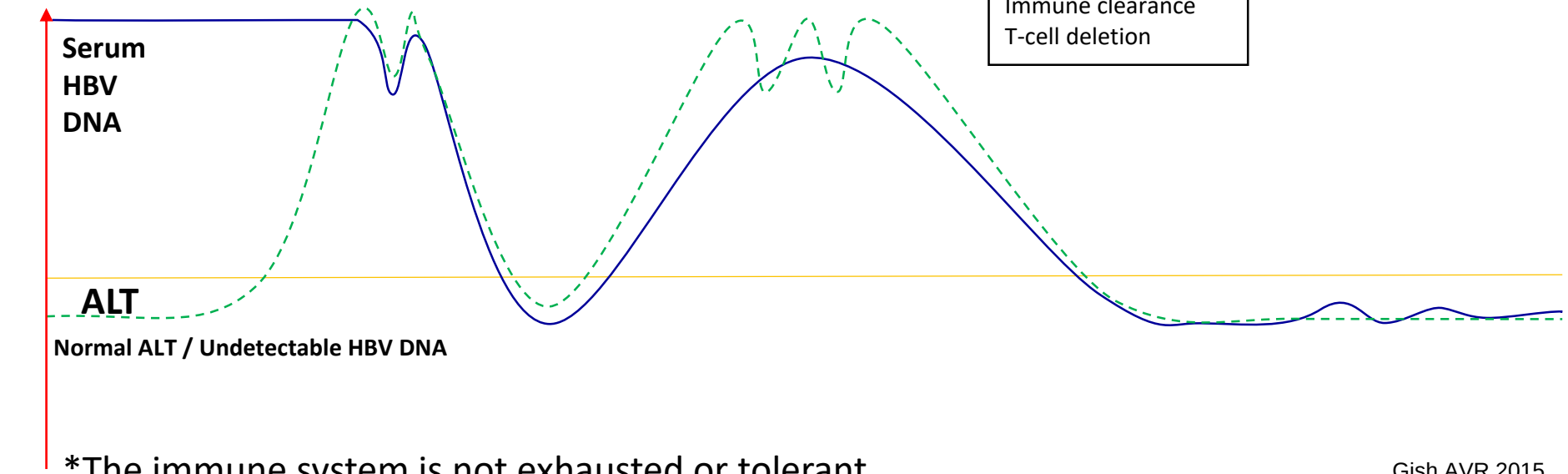
Chronic Infection Immune Control Inactive Dx Non-Replicative

- Low or undetectable HBV DNA
- HBeAg(-)
- Very low HBsAg levels
- Normal ALT
- May be seen after Immune clearance T-cell deletion

HBsAg(-) Loss/Occult Hepatitis B

- Serum HBV DNA phases, alternating undetectable and very low but detectable
- Detectable HBV DNA in the liver
- Intrahepatic replication-competent HBV genomes such as HBV cccDNA
- Integrated HBV DNA

Resolved infection



*The immune system is not exhausted or tolerant

Gish AVR 2015

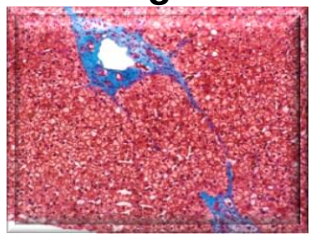
Progression of Fibrosis in Viral Hepatitis on Biopsy (Metavir)

No Fibrosis

Stage 1

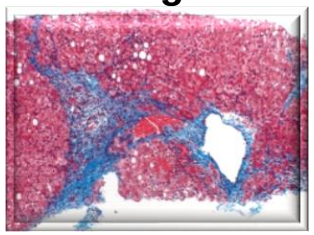
Fibrous expansion of some portal areas

Stage 2



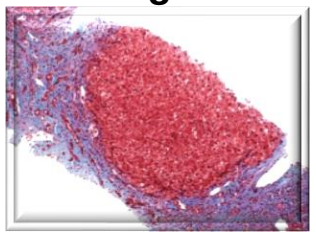
Fibrous expansion of most portal areas with occasional portal to portal bridging

Stage 3



Fibrous expansion of portal areas with marked bridging (portal-to-portal and portal-to-central)

Stage 4

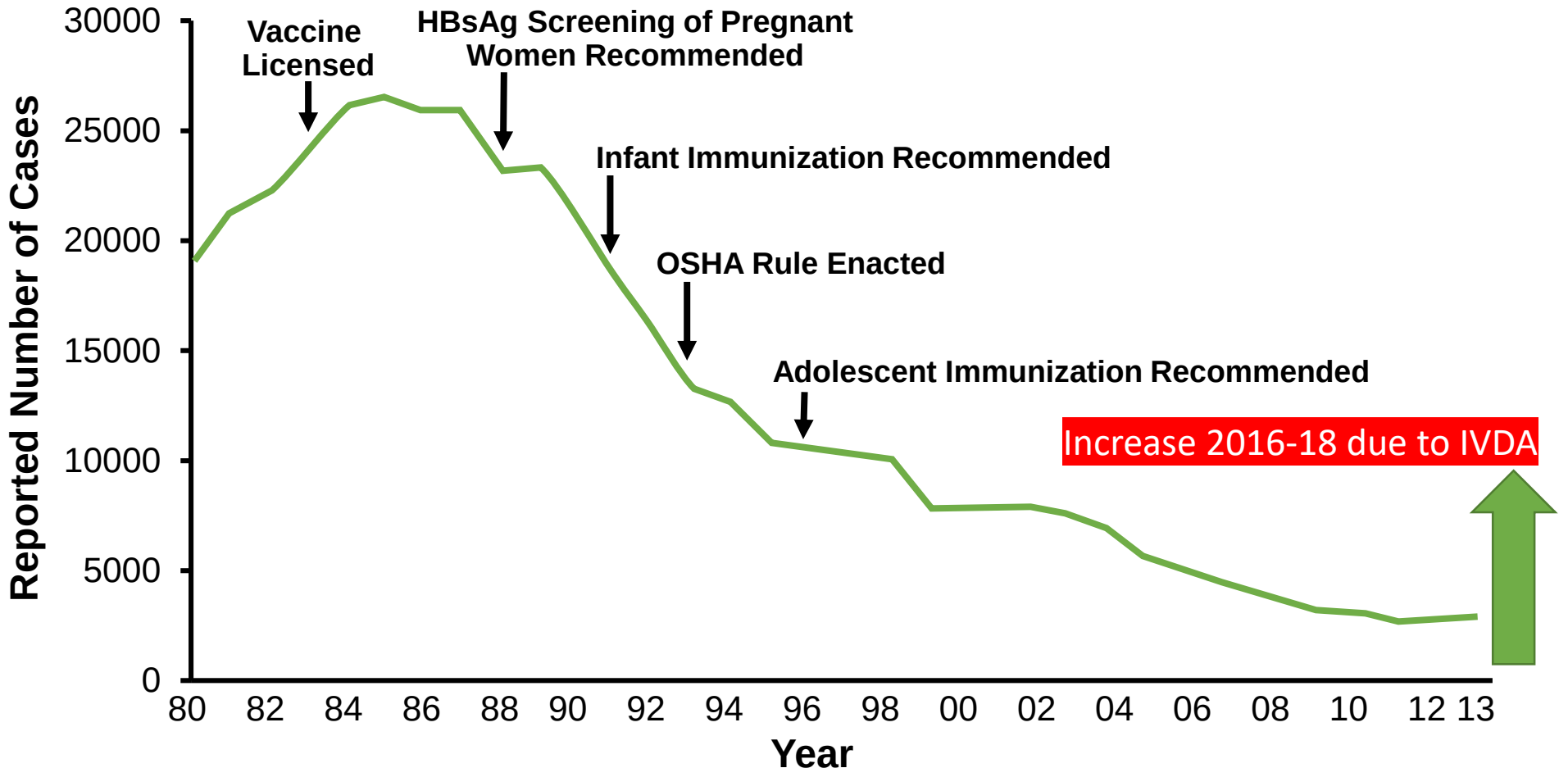


Cirrhosis

Cirrhotic Liver

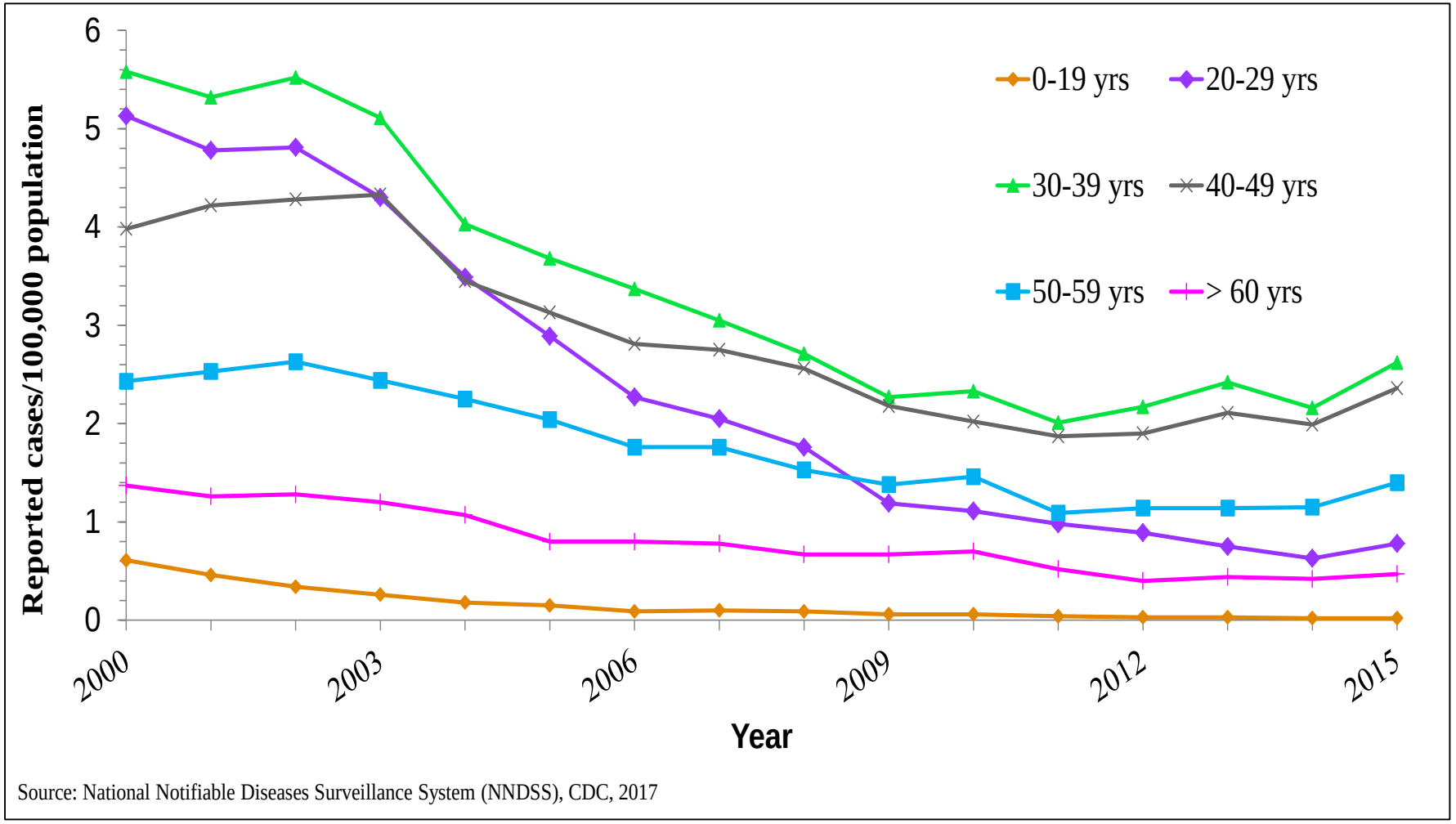
Faria SC, et al. *Radiographics.* 2009;29:1615-1635. Adapted from Everson GT.

New HBV Infections by Year: United States (1980-2013)



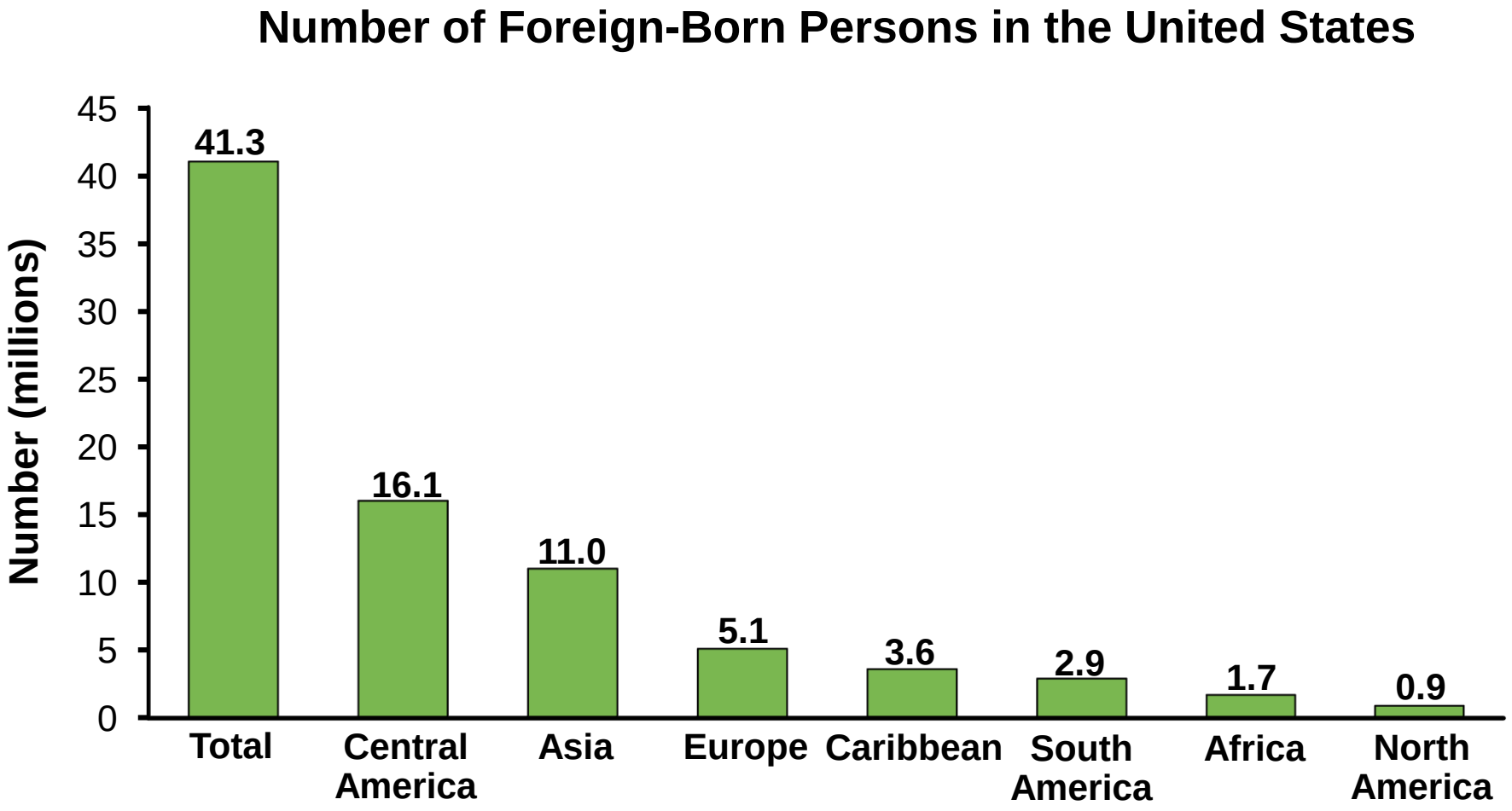
CDC. http://www.cdc.gov/hepatitis/hbv/hbvfaq.htm#overview.

Significant Need for Hepatitis B Protection in Adults; New cases of HBV by age



Source: National Notifiable Diseases Surveillance System (NNDSS), CDC, 2017

Foreign-Born Persons in the US: Overall and By Place of Birth (2009)



Kowdley KV, et al. *Hepatology.* 2012;56:422-433.

Geographic Diversity of HBV Infection: Clinical and Epidemiologic Correlations

	North America Western Europe	Sub-Saharan Africa Far East
Endemicity	Low	High
Age of infection	Early adulthood	Birth Toddler
Primary mode of transmission	Percutaneous Sexual	Perinatal Horizontal
Chronicity	Rare	Likely
Risk of end-stage liver disease	Low*	High
Risk of hepatocellular carcinoma	Low*	High

*Low for general population, but high among those HBsAg positive.

Institute of Medicine 2010: Barriers to Prevention and Control of HBV

- Lack of knowledge and awareness about chronic viral hepatitis among
  - Health-care and social-service providers
  - At-risk populations, members of the public, and policy makers
- Insufficient understanding about the extent and seriousness of this public-health problem
  - Lack of public resource allocation to prevention, control, and surveillance programs

Institute of Medicine. Available at: http://www.nap.edu/catalog/12793.html.

Institute of Medicine: Projected Outcomes

- Screening is widely used as a part of good primary care
- At-risk people and communities actively seeking testing, preventive services, and appropriate medical management
- Better information leads to:
  - Improved understanding of HBV and HCV
  - More effective and targeted prevention programs
  - More research on effective vaccination and treatment options
- Infected people have better health outcomes
- Decreased transmission leads to fewer carriers of HBV and HCV and fewer cases of HBV and HCV

Institute of Medicine. Available at: http://www.nap.edu/catalog/12793.html.

Rationale for Prompt Identification of HBV-Infected Persons

- Implement important interventions to reduce morbidity and mortality
  - Clinical evaluations to detect onset and progression of HBV-related liver disease
    - HBV DNA, HBeAg, ALT, HCC biomarker panel, imaging, APRI, FIB-4, transient elastography
  - Antiviral therapy can delay or reverse progression of liver disease
  - Detect HCC at a potentially treatable stage with baseline AFP and periodic ultrasound/biomarker surveillance
  - Implement interventions to reduce progression of liver injury
    - Hepatitis A vaccination
    - Counseling to avoid excessive alcohol use

Adapted from Weinbaum CM, et al. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.
Chaiteerakij R, et al. *Clin Gastroenterol Hepatol.* 2015;13:237-245.

Candidates for Screening for HBV?
HBV FOUNDATION : >>>>>EVERYONE

- Persons born in high and intermediate endemic areas (≥2% prevalence)
- US born children of immigrants from high-risk areas
- Household and sexual contacts of HBsAg-positive persons
- Persons who have ever injected drugs
- Persons with multiple sexual partner, or history of STDs
- Men who have sex with men
- Inmates of correctional facilities
- Individuals with chronically elevated ALT/AST
- Individuals infected with HIV or HCV
- Patients undergoing dialysis
- All pregnant women

Weinbaum CM, et al. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.
LeFevre ML on behalf of the U.S. Preventive Services Task Force. *Ann Intern Med.* 2014;161:58-66.

HBV Testing in Persons With a History of Vaccination

- HBsAg testing is recommended regardless of vaccination history for the following (consider anti-HBc and anti-HBs testing)
  - Persons born in geographic regions with HBV prevalence ≥2%
  - US-born persons not vaccinated as infants whose parents were born in regions with high HBV prevalence (≥8%)
  - Persons who receive HBV vaccination as adolescents or adults after initiation of risk behaviors
    - Men who have sex with men
    - Injection-drug use
- Patients with anti-HBc do not need vaccination nor “booster” doses

Weinbaum CM, et al. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.

Tests Used to Screen for HBV Infection

- HBsAg, anti-HBc and anti-HBs
  - If only an Anti-HBc positive result is found in the medical chart
    - Confirm testing for both HBsAg and anti-HBs are completed
- Isolated anti-HBc positive result, possible explanations
  - Indicator of low level chronic HBV infection if anti-HBs is negative
  - Marker of exposure after recovery from a prior infection
  - False positive test result (rare) 2:1000 tests
  - Acute HBV infection (if anti-HBc IgM+) or flare of CHB

Updated from : Lok AS, et al. *Hepatology*. 2009;50:661-662. Available at: http://www.aasld.org.

AASLD Guidance: HBeAg-Positive CHB

Noncirrhotic HBeAg-Positive Patients With CHB

ALT ≤ ULN

HBV DNA > 20,000 IU/mL

- **Monitor** ALT and HBV DNA every 3-6 mos, HBeAg every 6-12 mos

ALT > ULN but < 2 x ULN

HBV DNA > 20,000 IU/mL

- Exclude other causes of ALT elevation
  - **Treat if ALT elevation persists, especially if > 40 yrs of age**
- Evaluate fibrosis/inflammation
  - **Treat if ≥ F2/A2**

HBV DNA 2000-20,000 IU/mL may represent seroconversion

- **Monitor** HBV DNA every 1-3 mos
  - **Treat if HBV DNA > 2000 IU/mL persists for > 6 mos**

ALT ≥ 2 x ULN

HBV DNA > 20,000 IU/mL

- **Treat**

Terrault. Hepatology. 2018;67:1560.

Slide credit: clinicaloptions.com

AASLD Guidance: HBeAg-Negative CHB

Noncirrhotic HBeAg-Negative Patients With CHB

ALT ≤ ULN

HBV DNA ≥ 2000 IU/mL
- **Monitor** ALT and HBV DNA every 3 mos for 1 yr, then every 6 mos

HBV DNA < 2000 IU/mL
- **Monitor** ALT and HBV DNA every 3-6 mos
- **Monitor** HBsAg annually

ALT > ULN but < 2 x ULN

Any Detectable HBV DNA
- Exclude other causes of ALT elevation
  - **Treat if ALT elevation persists with HBV DNA ≥ 2000 IU/mL, especially if > 40 yrs of age**
- Evaluate fibrosis/inflammation
  - **Treat if ≥ F2/A2**

ALT ≥ 2 x ULN

HBV DNA ≥ 2000 IU/mL
- **Treat**

HBV DNA < 2000 IU/mL
- Exclude other causes of ALT elevation and evaluate fibrosis/inflammation
  - **Treat if ≥ F2/A2**

Terrault. Hepatology. 2018;67:1560.

Slide credit: clinicaloptions.com

Simplify Treatment

- HBV DNA > 2000 and
  - ALT over 20-25 in women over 30-35 in men
  - Elevated HCC biomarkers
  - Older age and active liver disease
  - High risk for HCC
  - Family hx of HCC
- HCC diagnosis
- Any patient with cirrhosis with any HBV DNA + level

2018 AASLD Guidance: Monitoring of CHB Patients Not on Antiviral Therapy

	Immune-Tolerant CHB	Inactive CHB	Resolved CHB
Definition of Population	HBeAg positive, high HBV DNA	HBeAg negative, normal ALT, low HBV DNA	HBsAg loss
Recommended Monitoring for Population	**ALT: every 3-6 mos** ▪ If ALT level rises to > ULN, evaluate ALT and HBV DNA more frequently **HBeAg status: every 6-12 mos** ▪ Treat if HBeAg+ with HBV DNA > 20,000 IU/mL for 3-6 mos and ALT > 2 x ULN **Liver biopsy or noninvasive assessment of fibrosis** ▪ Consider with slight, persistent ALT elevation, particularly if > 40 yrs of age and infected for long duration	**ALT and HBV DNA: every 3 mos for first yr, then every 6-12 mos** ▪ If ALT level rises to > ULN, evaluate ALT and HBV DNA more frequently **HBsAg: annually**	**ALT and HBV DNA monitoring no longer required** **HCC surveillance** ▪ Continue if individual has cirrhosis, a first-degree family member with HCC, or a long duration of infection

If treatment is not indicated, actively monitor as candidacy may change with disease progression

Terrault. Hepatology. 2018;67:1560. www.aasld.org.

Slide credit: clinicaloptions.com

AASLD Guidelines: Recommendations for HCC Surveillance

- Hepatitis B carriers at high risk[1]
  - All patients with cirrhosis
  - Patients with first-degree family member with history of HCC
  - Asian or black men older than 40 yrs of age
  - Asian women older than 50 yrs of age
  - Coinfected with HDV
- Liver ultrasound with or without AFP in high risk patients every 6 mos[1,2]

1. Terrault. Hepatology. 2018;67:1560. 2. Heimbach. Hepatology. 2018;67:358.

Slide credit: clinicaloptions.com

Efficacy and Limitations of Currently Available HBV Therapies

Efficacy

- Result in potent viral suppression
- Reverse hepatic fibrosis/cirrhosis
- Prevent progression to liver failure

Limitations

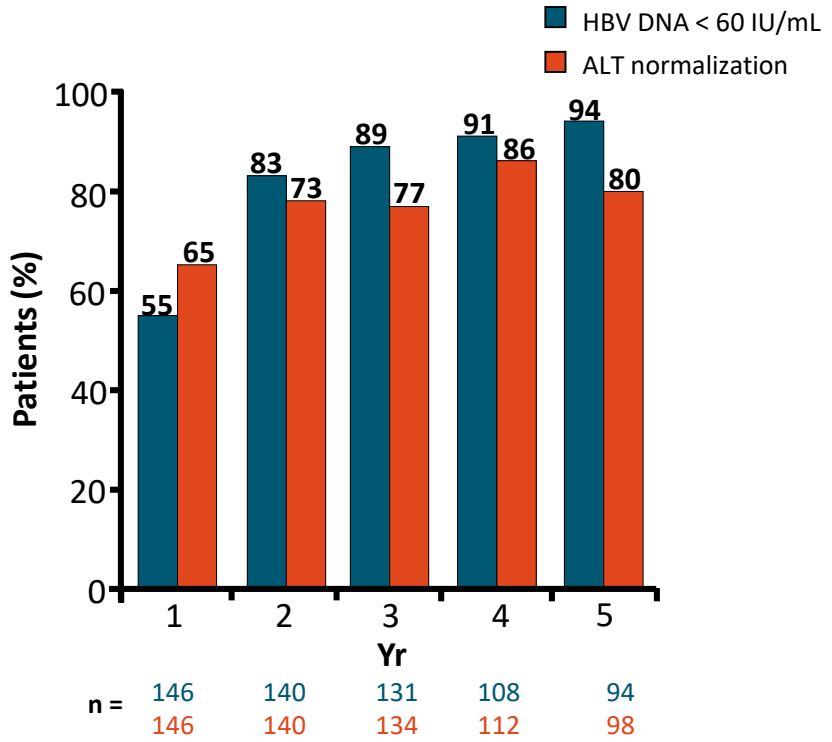
- Result in low rate of HBsAg loss
- Decrease but do not eliminate risk of HCC
- Require long duration (lifelong in some patients) to maintain benefit, resulting in high costs, potential drug resistance, and prolonged adverse events

EASL. J Hepatol. 2017;67:370.

Slide credit: clinicaloptions.com

Study ETV-901: 5-Yr Efficacy of Entecavir in HBeAg-Positive Patients

- Long-term observational roll-over study of patients from ETV-022 who were previously nucleoside naive (N = 146)
- Long-term ETV (1 mg QD) resulted in durable virologic suppression and maintenance of ALT normalization
- ETV resistance emerged in 1 patient (1%) with virologic breakthrough at Yr 3



Chang. Hepatology. 2010;51:422.

Slide credit: clinicaloptions.com

Studies 102/103: 8-Yr Efficacy of TDF

Outcome, %[1]	HBeAg-Negative (n = 375)		HBeAg-Positive (n = 266)	
	ITT*	Observed†	ITT	Observed
HBV DNA < 29 IU/mL	74	99	58	97
HBeAg				
▪ Loss	NA	NA	32	47
▪ Seroconversion			21	31
HBsAg‡				
▪ Loss	1.1	NA	12.9	NA
▪ Seroconversion	0.7		10.3	

*Missing or addition of FTC = failure. †Missing excluded; addition of FTC included. ‡Kaplan-Meier ITT.

TAF efficacy comparable to that of TDF with available data out to 96 wks[2,3] and 144 wks[4]

1. Marcellin. AASLD 2014. Abstr 299.
2. Agarwal. EASL 2017. Abstr FRI-153.
3. Brunetto. EASL 2017. Abstr PS-042.
4. Chan. AASLD 208. Abstr 235.

Chronic HBV Infection: Updated EASL Recommendations

Monotherapy with ETV, TAF, TDF recommended based on high barrier to resistance

- PegIFN should only be considered as initial treatment for pts with mild/moderate CHB or selected pts with compensated cirrhosis (no portal hypertension)

ETV or TAF Preferred Over TDF When:
Older than 60 yrs of age
Bone disease ▪ Chronic steroids or other meds that affect bone ▪ History of fragility fracture ▪ Osteoporosis
Renal abnormalities ▪ eGFR < 60 min/mL/1.73 m^2 ▪ Albuminuria > 30 mg or moderate proteinuria ▪ Low phosphate (< 2.5 mg/dL) ▪ Hemodialysis
TAF over ETV if previous NA exposure *No dose adjustment required for kidney disease or hemodialysis with TAF; ETV needs dose adjustment for eGFR < 50 mL/min*

Management of NA Resistance	
LAM resistance	Switch to TDF or TAF
TBV resistance	Switch to TDF or TAF
ETV resistance	Switch to TDF or TAF
ADV resistance	**LAM naive** ▪ Switch to ETV or TDF or TAF **LAM-R** ▪ Switch to TDF or TAF
TDF or TAF resistance	**LAM naive** ▪ Switch to ETV **LAM-R** ▪ Add ETV
Multidrug resistance	Switch to ETV + TDF or TAF combination

EASL. HBV guidelines. 2017.

HBV Vaccination

- Strategies to fight HBV infection
  - Treat patients with chronic HBV infection
  - Interrupting the route of transmission
  - Immunize susceptible individuals
  - Birth dose of HBV vaccine <24 hours from birth

- Vaccination is the most effective strategy to prevent individuals from contracting HBV infection

Locarnini S, et al. *J Hepatol.* 2015;62(suppl):S76-S86.

Vaccination at Time of Testing

- Patients in settings in which universal vaccination is recommended
  - STD/HIV testing and treatment facilities
  - Drug-abuse treatment and prevention settings
  - Health-care settings targeting services to
    - Injection-drug use
    - Men who have sex with men
  - Correctional facilities
- Administer first dose of vaccine at the same medical visit after blood is drawn for testing (with HBsAg, anti-HBc, and anti-HBs)
  - Unless an established patient-provider relation can ensure patient will return for serologic test results and initiation of vaccination
- Venues where vaccination is recommended but testing is not feasible

Weinbaum CM, et al. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.

Simplified: 6 Pillars of HBV

- Test all adults, all immigrants, all patients with unknown HBV vaccine status
- Anti-HBc = exposure, no vaccine, educate about reactivation risk (anti-HBc false + rate is 2/1000 in low risk patients)
- Vaccinate all adults who are triple panel negative
- ALT over ULH (upper limits of healthy) or +fibrosis (APRI, FIB4, TE or bx) and + DNA over 2000 = Nuc treatment,
  - cirrhosis and any HBV DNA = Nuc treatment
- Treat until HBsAg loss + 12 months consolidation
- Treatment changes outcomes !

Resources for your practice:

- Hepatitis B Management Guidance for the Primary Care Provider,
- https://www.hepatitisb.uw.edu/page/primary-care-workgroup/guidance

- Fact Sheets for patients
- https://www.cdc.gov/knowhepatitisb/materials.htm

- Hepatitis B Foundation Consultation Line, info@hepb.org, 215-489-4900,

- Interests in the Philadelphia Hepatitis B Programs? Catherine.Freeland@hepb.org

Thank You!

Robert Gish MD, FAASLD, AGAF, FAST

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Hepatitis B Foundation - Medical Director

Adjunct Professor of Medicine:

University of Nevada Las Vegas

University of Nevada Reno

UCSD Skaggs School of Pharmacy and Pharmaceutical Sciences

Questions?

Please type your questions into the Q&A box.

Christine Simon
csimon@phmc.org

NEW RESOURCE

Hepatitis C Virus (HCV) Cost Calculator

Our HCV Cost Calculator uses a numerical value-based model of health center staff training, screening, and treatment regimen to estimate the cost-benefit comparison and return on investment (ROI) to the health center.

No cost to use on NURSELEDCARE.ORG

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