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Hepatitis Viruses

Infectious Diseases/Microbiology Sequence Course

M1 Infectious Diseases Sequence Course

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Spring 2010

University of Michigan
Medical School

Objectives

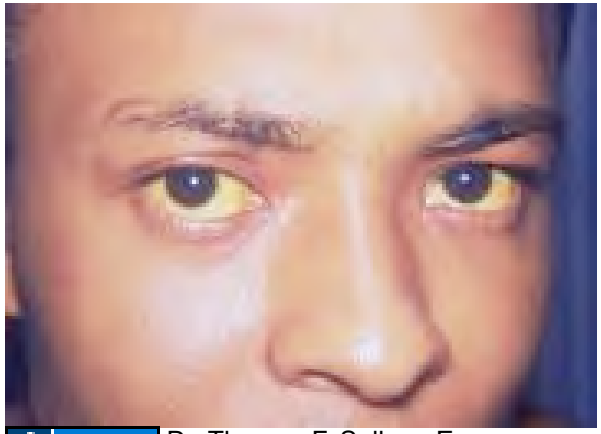
- **Know the different viruses that cause hepatitis**
- **Appreciate the differences between hepatitis virus genome structures and replication strategies**
- **Understand the differences between acute and chronic hepatitis**
- **Know the different transmission modes for hepatitis viruses**
- **Know the methods to diagnose hepatitis virus infections**
- **Understand the role of vaccination in the prevention of hepatitis virus infections**

Reading assignment: Schaechter's 4th edition, chapter 43

Hepatitis viruses

	Virology		Transmission			Treatment/Prevention		
	Structure	**Family**	**Fecal-oral**	**Sexual-parenteral**	**Vertical**	**Chronic infection**	**Antiviral Rx**	**Vaccine**
HAV	+ssRNA	*Picornaviridae*	Yes	Maybe	No	No	No	Yes
HBV	"dsDNA" enveloped	*Hepadnavirdae*	No	Yes	Yes	Yes	Yes	Yes
HCV	+ssRNA enveloped	*Flaviviridae*	No	Yes	Yes	Yes	Yes	No
HDV	-ssRNA "enveloped"	*Deltaviridae*	No	Yes	Yes	Yes	No	"No"
HEV	+ssRNA	*Hepeviridae*	Yes	Maybe	No	*No (except transplants)*	No	No

43 year old male traveled to Thailand on a business trip. He participated in some of the illicit evening “activities” and didn’t bother to use condoms. Three months later he developed fatigue and mild abdominal pain, and his wife noticed that his eyes were yellow. He didn’t seek medical attention and his symptoms resolved over the next month. However, his wife developed similar symptoms one month later, but these also resolved spontaneously. Twenty years later, she began suffering night sweats, weight loss, and abdominal pain over six months, and was eventually diagnosed with liver cancer.



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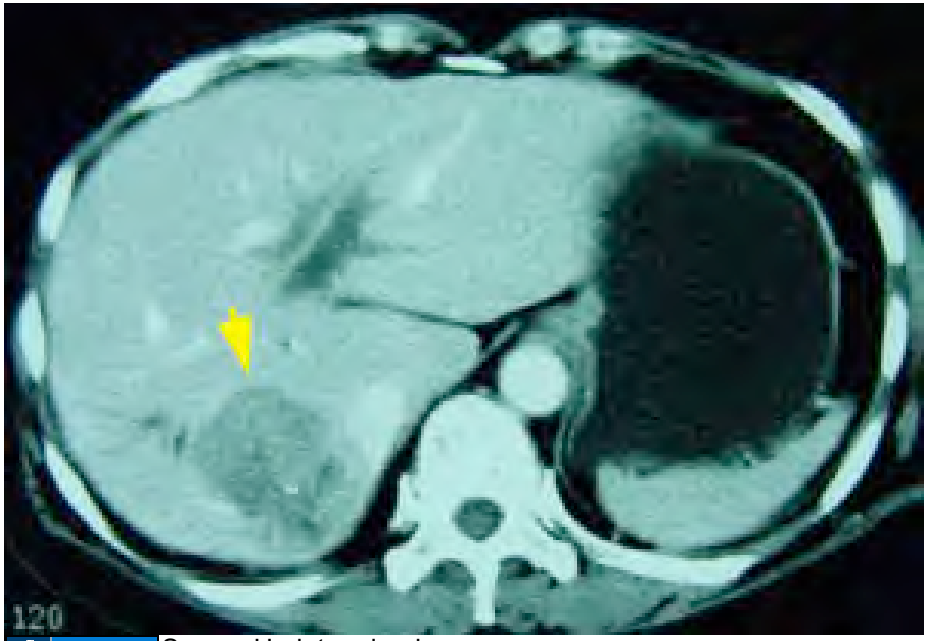

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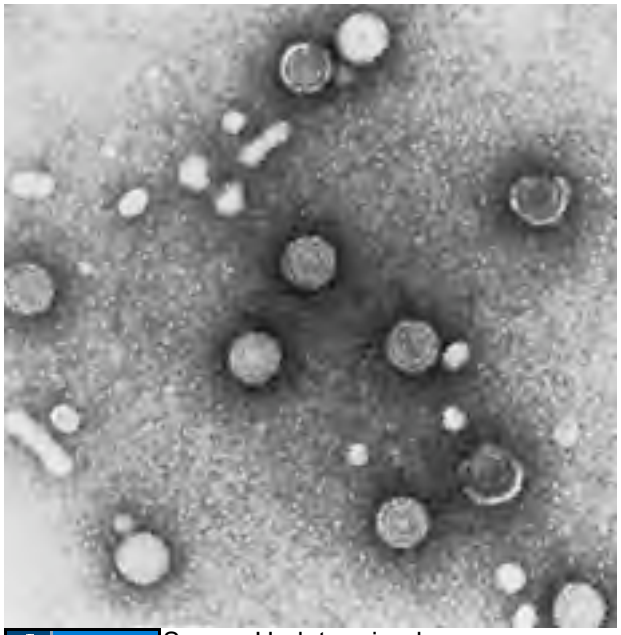
43 year old male traveled to *Thailand* on a business trip. He participated in some of the *illicit evening "activities"* and didn't bother to use condoms. *Three months later* he developed *fatigue and mild abdominal* pain, and his wife noticed that his *eyes were yellow*. He didn't seek medical attention and his *symptoms resolved* over the next month. However, his *wife developed similar symptoms* one month later, but these also resolved spontaneously. *Twenty years later*, she began suffering night sweats, weight loss, and abdominal pain over six months, and was eventually *diagnosed with liver cancer*.

Diagnosis?

Hepatitis B virus (HBV)

- **Family: *Hepadnaviridae***
- **Enveloped, partially double-stranded DNA virus**
- **Smallest genome of any human virus (3200 nt)**
- **Complex replication cycle**



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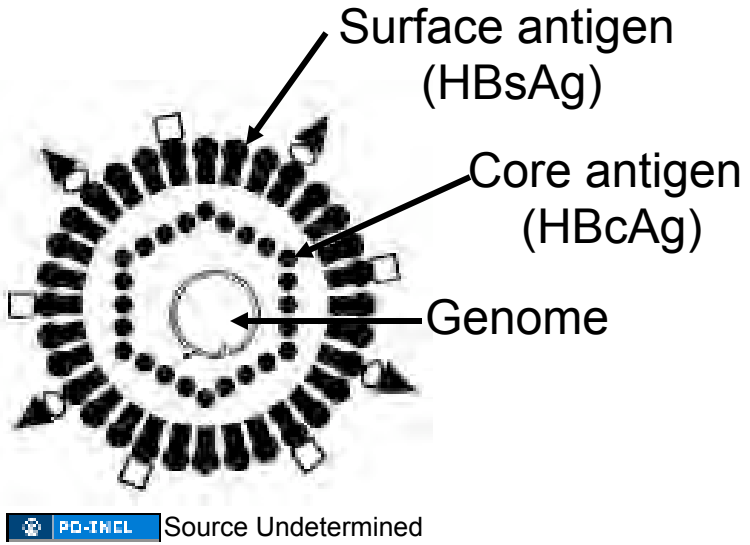

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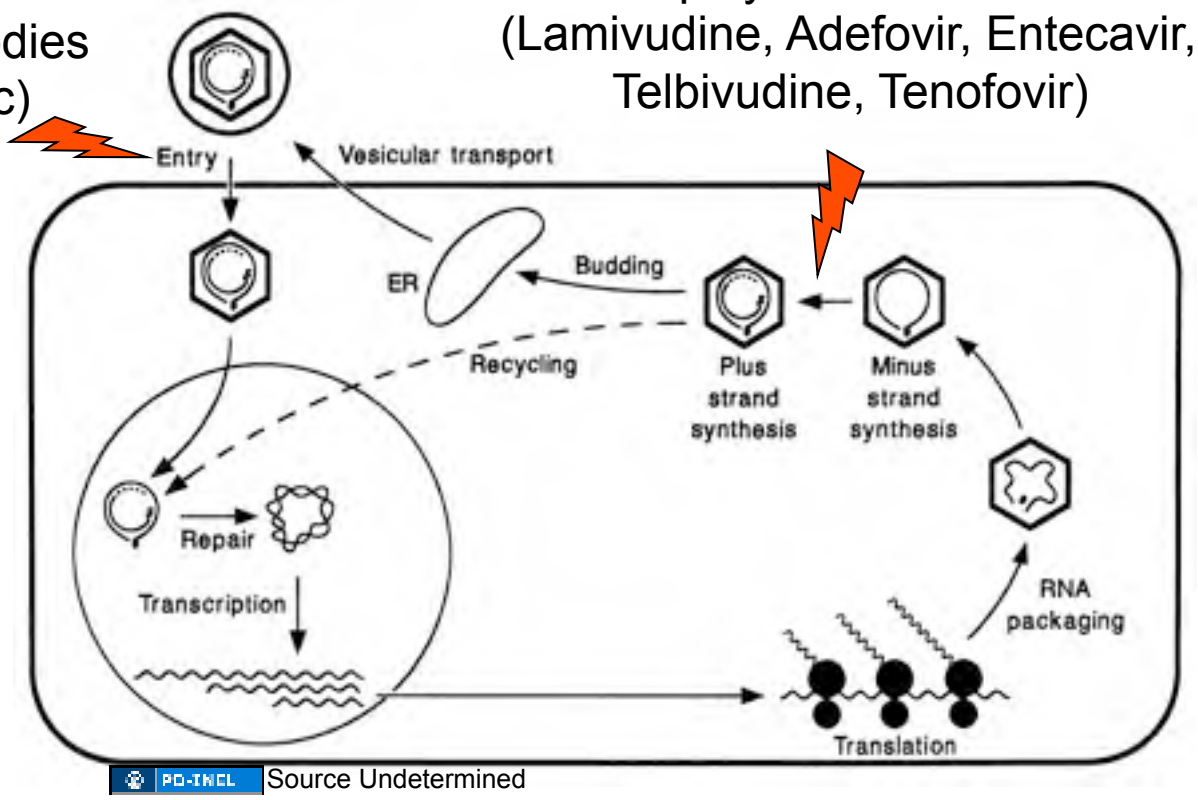
HBV life cycle

Neutralizing antibodies
(HBsAg-specific)

HBV polymerase inhibitors
(Lamivudine, Adefovir, Entecavir,
Telbivudine, Tenofovir)

- **Hepatocyte-specific receptor**
- **Nuclear steps require liver-specific elements**
- **Reverse transcription**
  - Essential for virion formation
  - Integration *NOT* essential (contrast to retroviruses)



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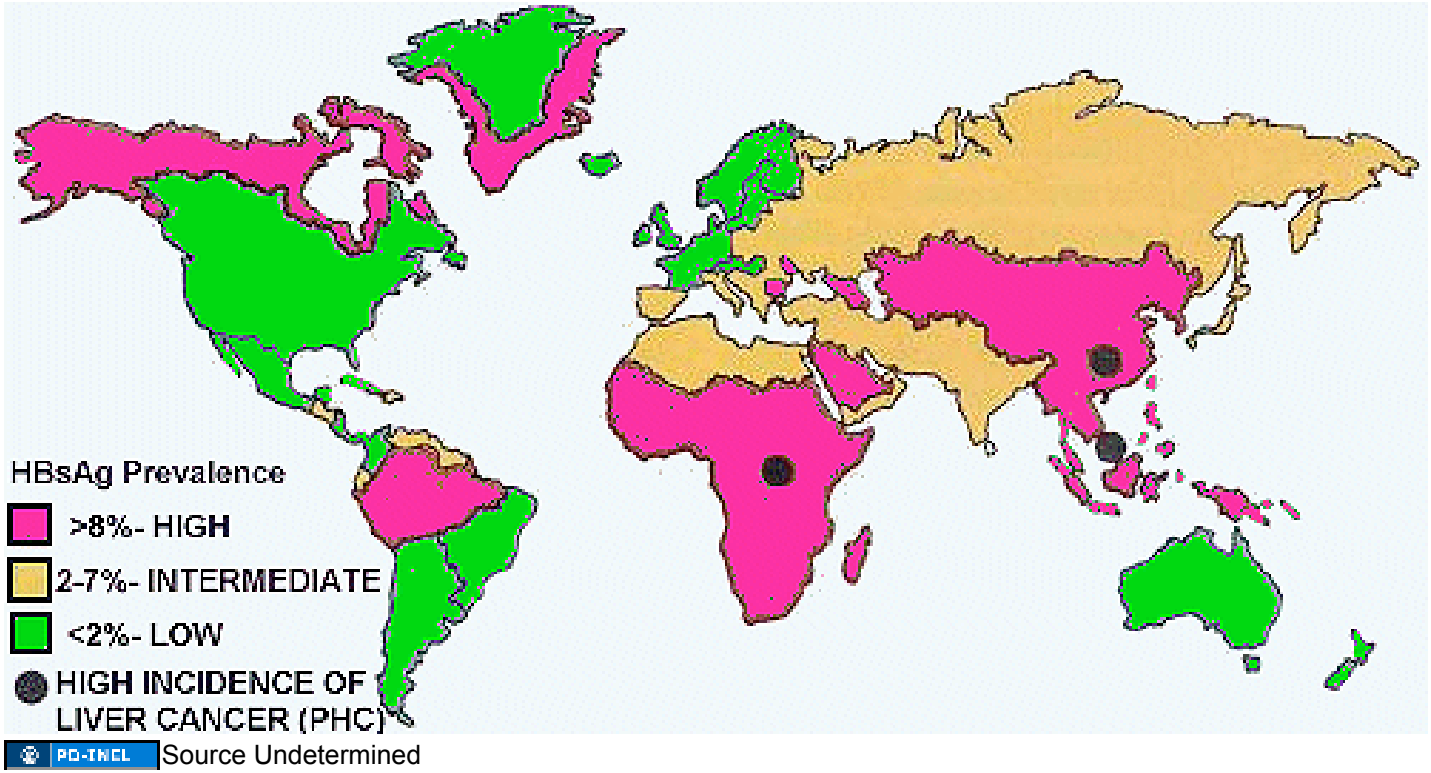
HBV Epidemiology

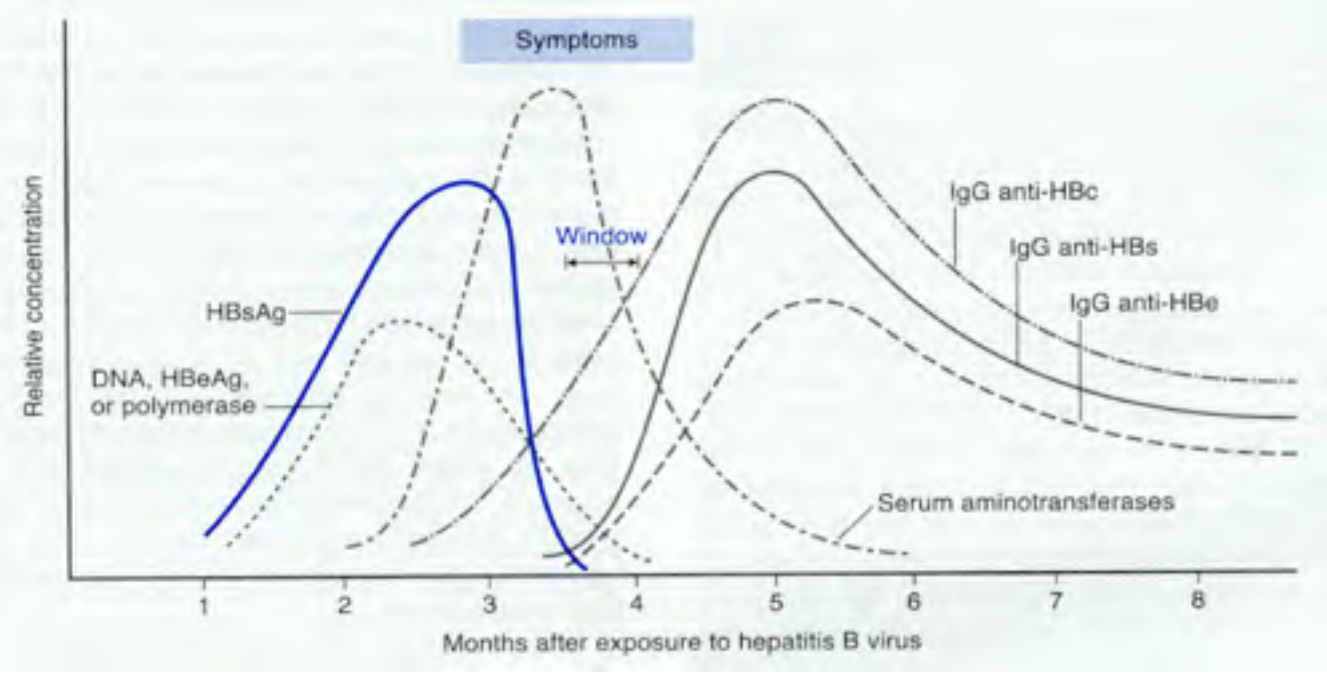


- **Enormous disease burden worldwide**
  - One-third of the world's population exposed
  - More than 300 million people with chronic infection

HBV Clinical Manifestations

- **Transmission**
  - Parenteral (sexual, IVDU, transfusion, transplant)
  - Vertical
- **Primary symptoms**
  - 6-26 week incubation period
  - Symptoms parallel immune response
  - 95% clear infection *(contrast to HCV)*
- **Complications**
  - 5% progress to chronic infection
    - Immunosuppressed and newborns have increased risk
  - 100-fold increase in HCC after several decades

HBV Diagnosis



	HBsAg	Anti-HBs	Anti-HBc	HBeAg/PCR
Vaccination	–	+	–	–
Acute infection	+	–	+/–	+
Prior infection, resolved	–	+	+	–
Chronic, inactive	+	–	+	–
Chronic, active	+	–	+	+

HBV Treatment

- Most effective for chronic active infection
- Interferon α
- HBV polymerase (RT) inhibitors (originally developed for HIV)
  - Lamivudine - resistance frequent
  - Adefovir – resistance uncommon
  - Entecavir - active against Lamivudine-resistant strains
  - Telbivudine
  - Tenofovir (FDA approved in August, 2008)
    - Often combined with emtricitabine (Truvada, Atripla)

HBV Prevention

- **Active immunization**
  - Recombinant subunit vaccine produced in yeast (HBsAg)
  - Combination vaccine with HAV available (Twinrix)
  - Highly effective
  - Component of routine childhood vaccine series
  - Recommended for high risk adults
    - Health care and long-term care facility workers, HD patients, IVDU, MSM, commercial sex workers, HIV infection, recent STD, travelers, chronic liver disease
  - Seroconversion rate declines with age and immunosuppression
    - >95% for age < 30 yo, but only 50% for age > 60 yo

- **Passive immunization**
  - Immune globulin available for post-exposure prophylaxis

Hepatitis D virus (HDV)

- **Family: *Deltaviridae***
- ***Not true virus***
  - ssRNA genome, but no envelope protein genes
  - Requires HBV co-infection for propagation
- **Associated with increased disease severity**
  - Higher mortality with acute infection
  - Greater risk for chronic complications
- **HBV vaccine protects against HDV infection**

18 year old female college student gave into peer pressure and decided to experiment with intravenous heroin. She had no problems after waking up from her drug-induced stupor, but didn't care much for the experience and never tried it again. Fifteen years later she noticed that her belly was getting larger fairly quickly, even though she was eating less because of generally feeling poorly. Her physician diagnosed her with ascites secondary to liver cirrhosis. Over the next two years she had repeated hospitalization due to ascites, spontaneous bacterial peritonitis (SBP), and bleeding problems. Even though she was placed on the liver transplantation list, she died from liver failure while awaiting an organ.

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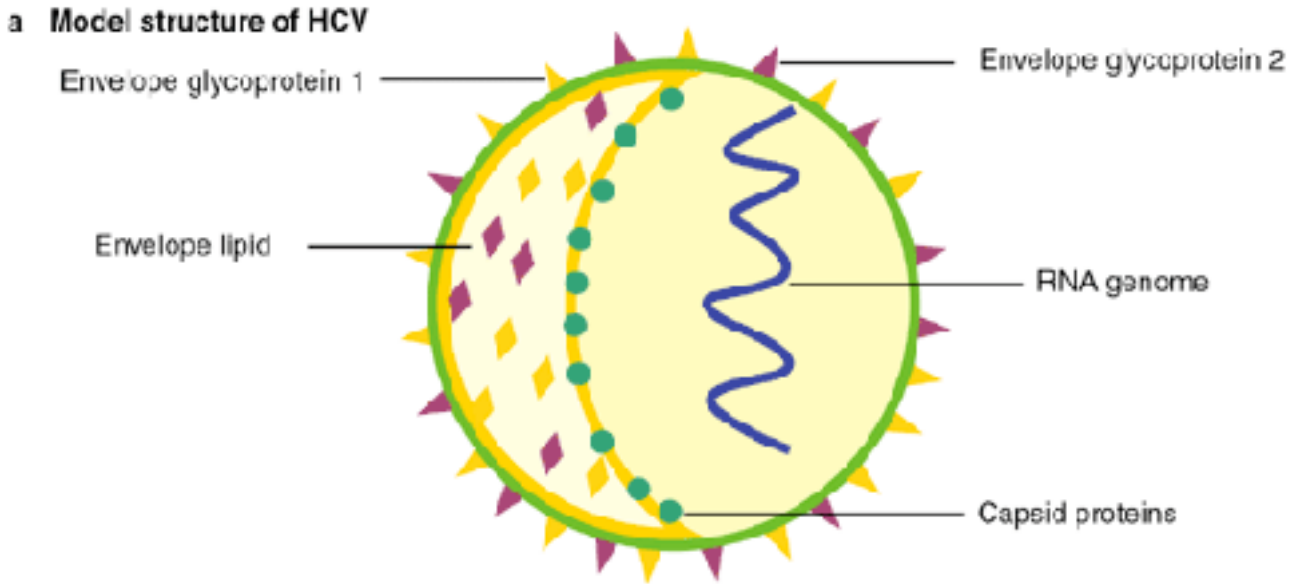
18 year old female college student gave into peer pressure and decided to experiment with *intravenous heroin*. She had no problems after waking up from her drug-induced stupor, but didn't care much for the experience and *never tried it again*. *Fifteen years later* she noticed that her *belly was getting larger* fairly quickly, even though she was eating less because of *generally feeling poorly*. Her physician diagnosed her with *ascites secondary to liver cirrhosis*. Over the next two years she had *repeated hospitalization due to ascites, spontaneous bacterial peritonitis (SBP), and bleeding problems*. Even though she was placed on the *liver transplantation list*, she *died from liver failure* while awaiting an organ.

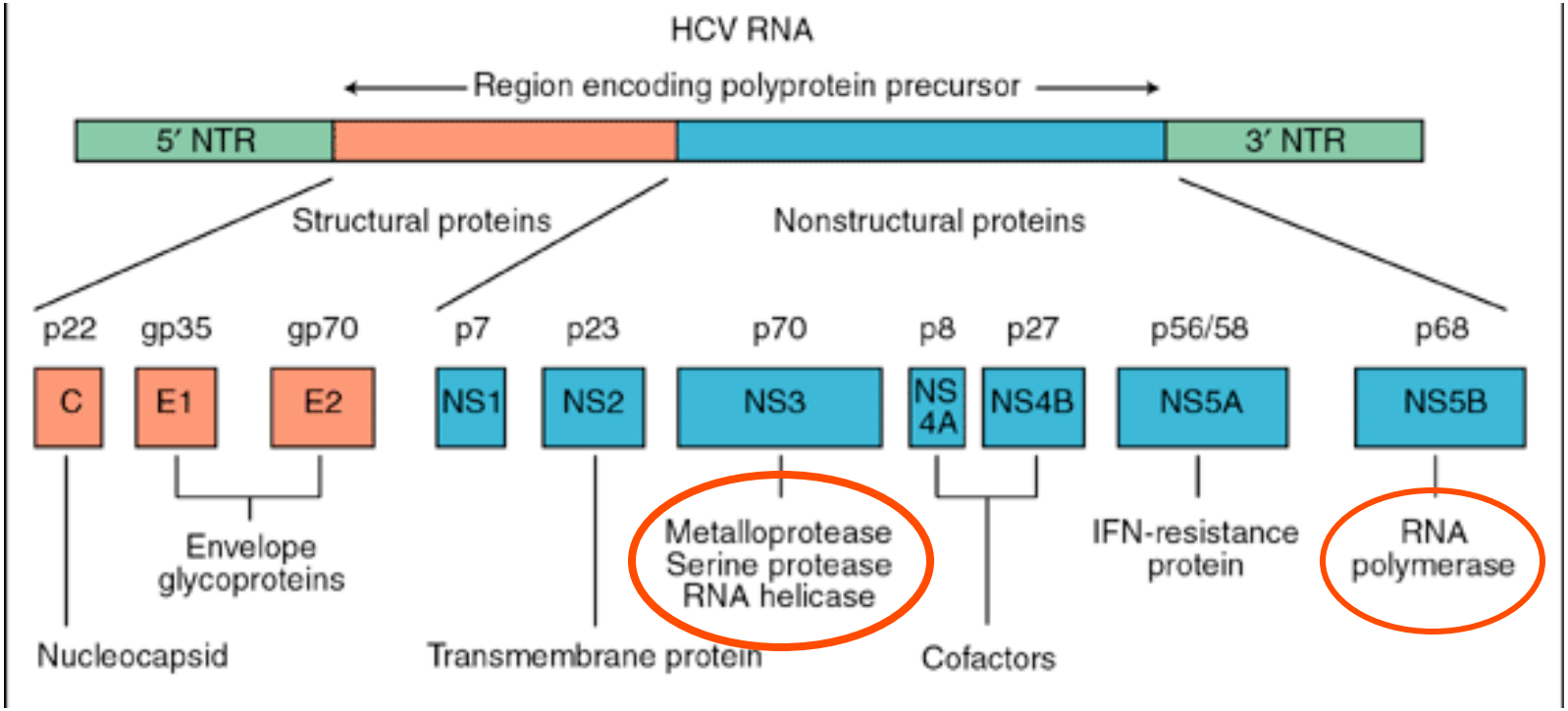
Diagnosis?

Hepatitis C virus (HCV)

- **Family: *Flaviviridae***
- **Enveloped**
- **Non-segmented positive (+) strand RNA genome**



HCV genome



Active drug targets

HCV Clinical Manifestations

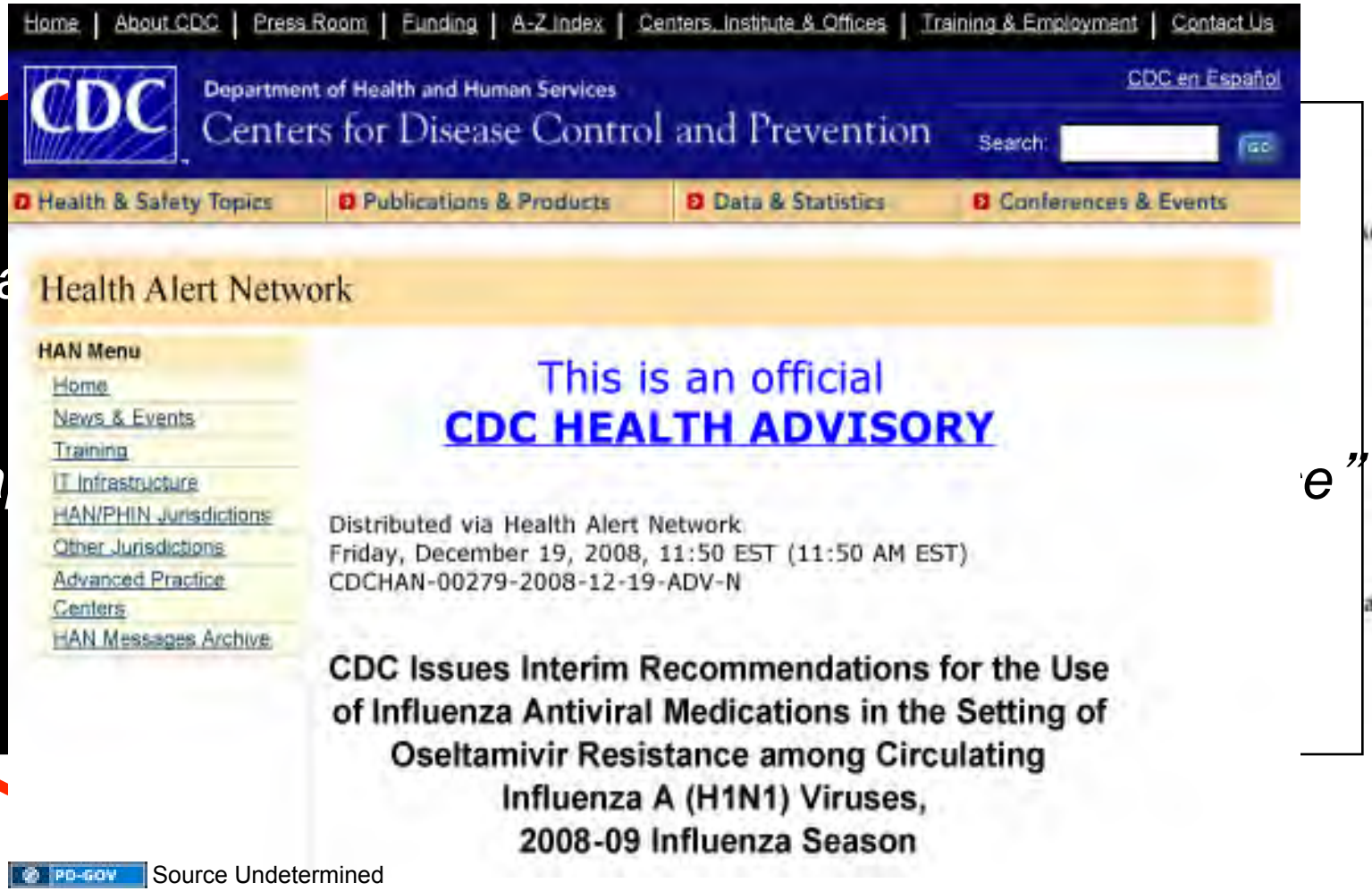
- **Transmission**
  - IVDU, sexual (less than HBV), transfusion, transplant
  - Vertical
- **Primary symptoms**
  - Acute infection often asymptomatic
  - Only 20% clear infection *(contrast with HBV)*
- **Complications**
  - 70-80% progress to chronic infection
  - 20% will develop cirrhosis (over 20 years)
  - HCC risk increased (1-4% per year)
  - Extrahepatic manifestations
    - Mixed cryoglobulinemia

HCV Diagnosis and Treatment

- **Diagnosis**
  - Serologies
  - Viral genome detection (RT-PCR)

- **Treatment**
  - Interferon α (frequent adverse reactions)
  - Ribavirin
    - Rapid resistance if use alone
  - Combination therapy most effective (IFNα + Rib)
    - <50% sustained response
  - Active area of investigation for new targets/drugs
    - R7128 and IDX184 - polymerase inhibitors
    - VX-950 (Telaprevir) - protease inhibitor
    - Debio-025 – cyclophilin inhibitor
  - Liver transplantation

Potential targets for antivirals



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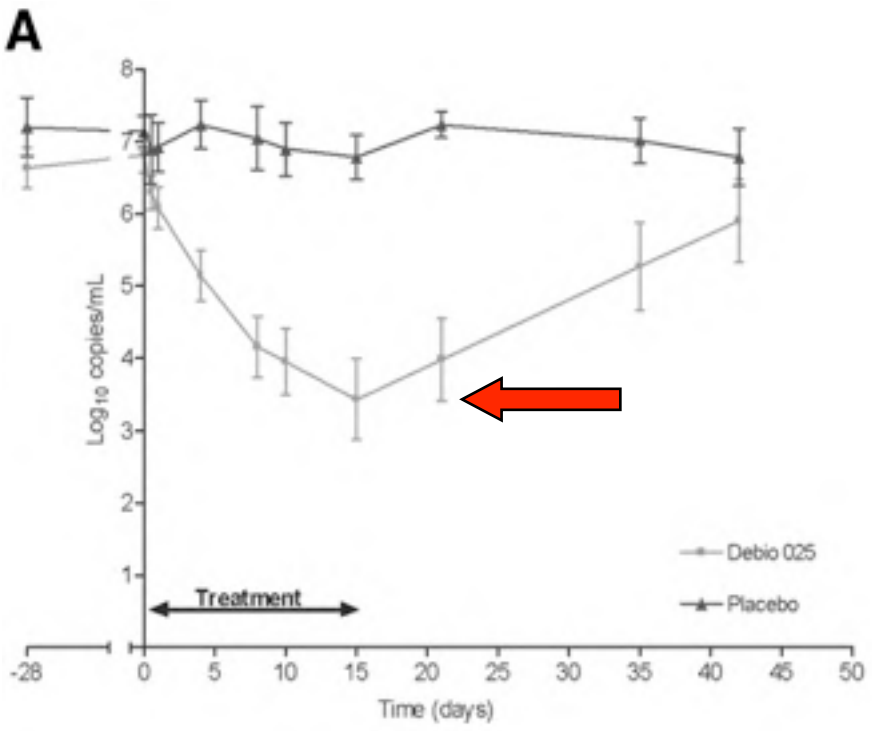
The Cyclophilin Inhibitor Debio-025 Shows Potent Anti–Hepatitis C Effect in Patients Coinfected with Hepatitis C and Human Immunodeficiency Virus

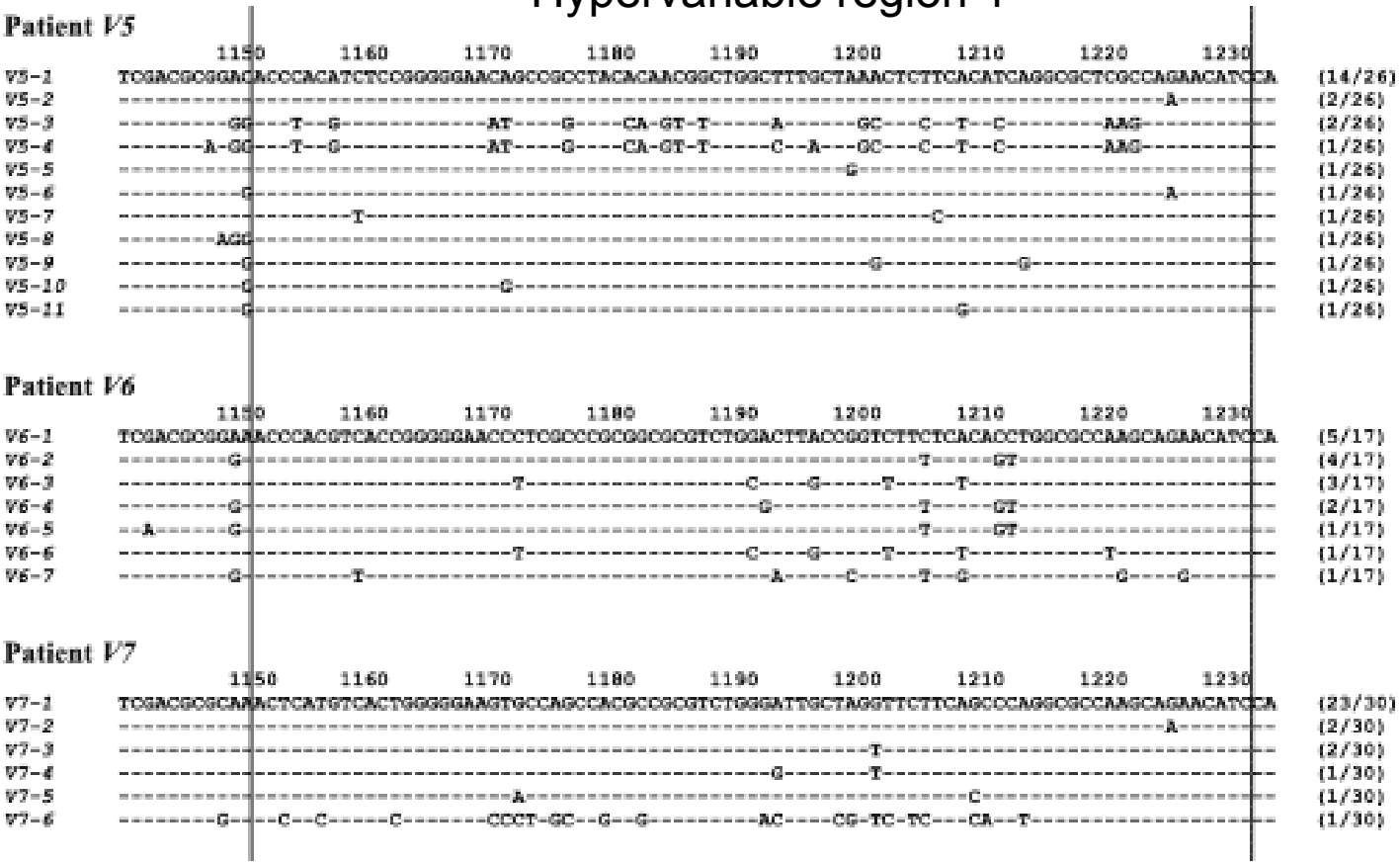
Robert Flisiak,[1] Andrzej Horban,[2] Philippe Gallay,[3] Michael Bobardt,[3] Suganya Selvarajah,[3] Alicja Wiercinska-Drapalo,[1] Ewa Siwak,[1] Iwona Cielniak,[2] Jozef Higersberger,[2] Jarek Kierkus,[1] Christian Aeschlimann,[3] Pierre Grosgurin,[3] Valérie Nicolas-Métral,[4] Jean-Maurice Dumont,[3] Hervé Porchet,[5] Raf Crabbé,[3] and Pietro Scalfaro[3]



HCV Prevention

Why is there no HCV vaccine?

Hypervariable region 1



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Viral Quasispecies

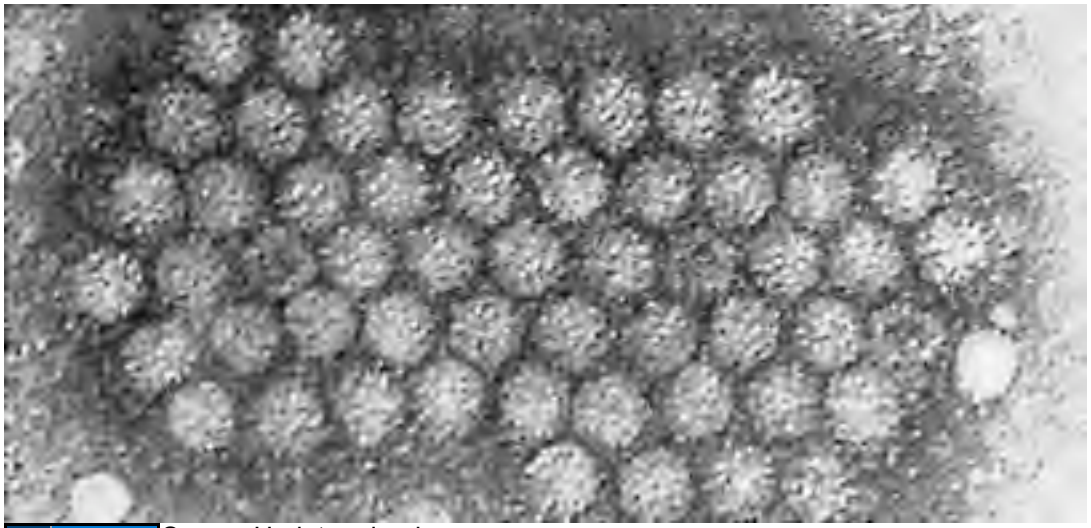
22 year old male college student went to Haiti as a Peace Corp volunteer for one week. He had philosophical issues with vaccines, and declined pretravel vaccinations. While in Haiti, he ate the local food and never boiled his water or used chlorine tablets. Three weeks after returning to the states he developed abdominal pain, nausea, vomiting, and jaundice. His symptoms resolved spontaneously, but one of his co-workers in the college cafeteria developed similar symptoms. Over the next three weeks, 20 college students who routinely ate at the cafeteria became ill, and the State Health Department was contacted immediately. Everyone eventually recovered without problems.

22 year old male college student went to *Haiti* as a Peace Corp volunteer for one week. He had philosophical issues with vaccines, and *declined pretravel vaccinations*. While in Haiti, he *ate the local food* and *never boiled his water or used chlorine tablets*. Three weeks after returning to the states he developed *abdominal pain, nausea, vomiting, and jaundice*. His symptoms *resolved spontaneously*, but one of his *co-workers in the college cafeteria developed similar symptoms*. Over the next three weeks, *20 college students who routinely ate at the cafeteria became ill*, and the *State Health Department was contacted* immediately. Everyone eventually recovered without problems.

Diagnosis?

Hepatitis A virus (HAV)

- **Family: *Picornaviridae***
  - Other members: poliovirus, rhinovirus
- **Non-enveloped (acid stable)**
- **Non-segmented positive (+) strand RNA genome**



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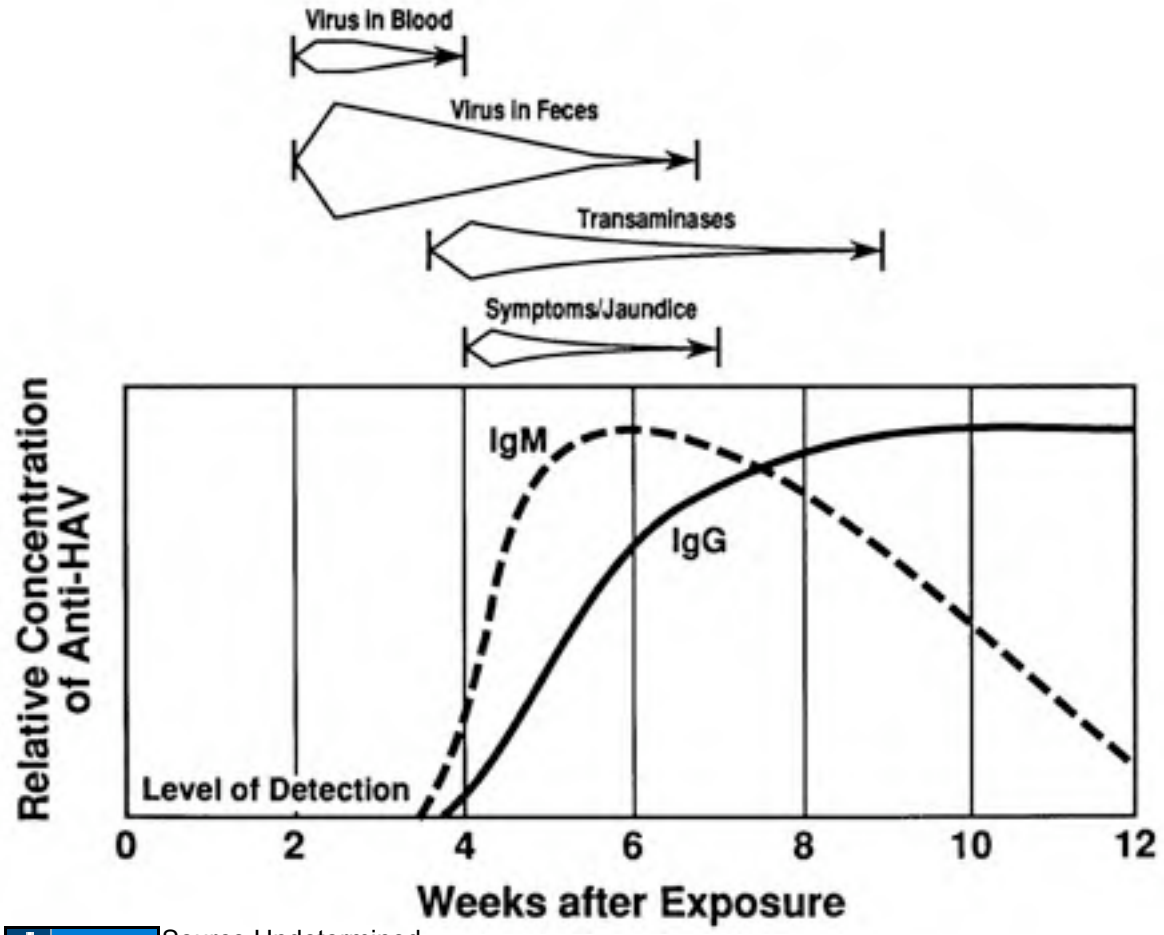
HAV Clinical Manifestations

- **Transmission**
  - Fecal-oral (extremely stable virus)
  - More common in underdeveloped countries
- **Primary infection**
  - Frequently symptomatic
  - Due to direct hepatocyte damage
- **Complications**
  - Fatal acute hepatitis rare
  - No chronic infection *(contrast to HBV and HCV)*

HAV Diagnosis



Serologic diagnosis

HAV Treatment and Prevention

- **Treatment**
  - None
  - Containment (limit transmission)

- **Prevention**
  - Natural infection produces lasting immunity
  - Inactivated vaccine available (Havrix, VAQTA)
    - Extremely effective (lasts >10 years)
    - Combination vaccine with HBV (Twinrix)

      May 2006, recommended for routine childhood vaccination (http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5507a1.htm)
    - Other indications: travel, chronic liver disease, MSM, IVDU
  - Immune globulin available for passive prophylaxis

Hepatitis E virus (HEV)

- **Family: *Hepeviridae (related to Caliciviridae)***
  - Non-enveloped, positive (+) sense RNA virus
- **Similar to HAV**
  - Fecal-oral transmission
  - More frequent in underdeveloped countries
  - Generally no chronic infection in normal patients
  - *Emerging as chronic pathogen in liver transplant patients (NEJM 358:811, 2008)*
- **Potentially life-threatening in pregnant women**
- **No vaccine currently available**

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Slide 7: Dr. Thomas F. Sellers, Emory University CDC PHIL #2860; Source Undetermined
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