

# Hepatitis C Natural History suggests that a vaccine is feasible and that much HCC is preventable

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# Hepatitis Viruses – we’re focused on “C” today

Hepatitis = inflammation of the liver

| Virus                          | Mode of transmission                   | Vaccine?                 |
|--------------------------------|--|--------------------------|
| Hepatitis A virus (HAV)        | Fecal – oral (food/water borne)        | Yes                      |
| Hepatitis B virus (HBV)        | Sex, drugs, mother-to-newborn          | Yes                      |
| <b>Hepatitis C virus (HCV)</b> | <b>Skin penetration, MSM+HIV, MTCT</b> | <b>No</b>                |
| Hepatitis D viroid (“delta”)   | Like HBV                               | Prevented by HBV vaccine |
| Hepatitis E virus (HEV)        | Fecal – oral (food/water borne)        | No (China has one)       |

# Hepatitis C virus (HCV)

- HCV was not discovered until 1989
- Transfusion was a major source of HCV infection prior to 1994
- Initial infection is without symptoms in more than 90%
  - 1/3 spontaneously clear HCV
  - 2/3 become persistently infected with HCV
- Chronic hepatitis causes liver inflammation
- Liver inflammation can cause scarring, eventually liver failure



D. Thomas (JHU)



P. Duggal (JHU)

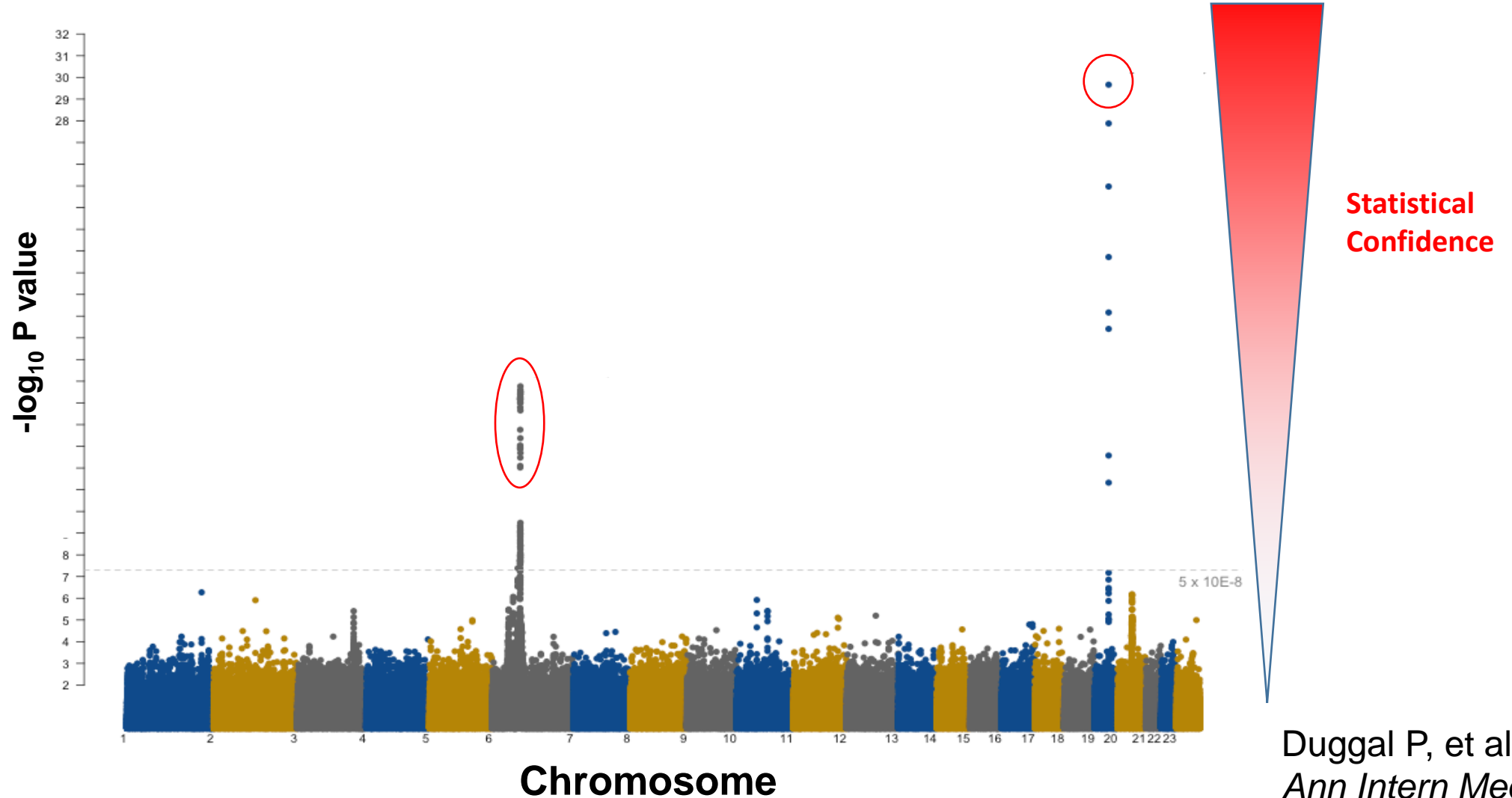


C. Thio (JHU)



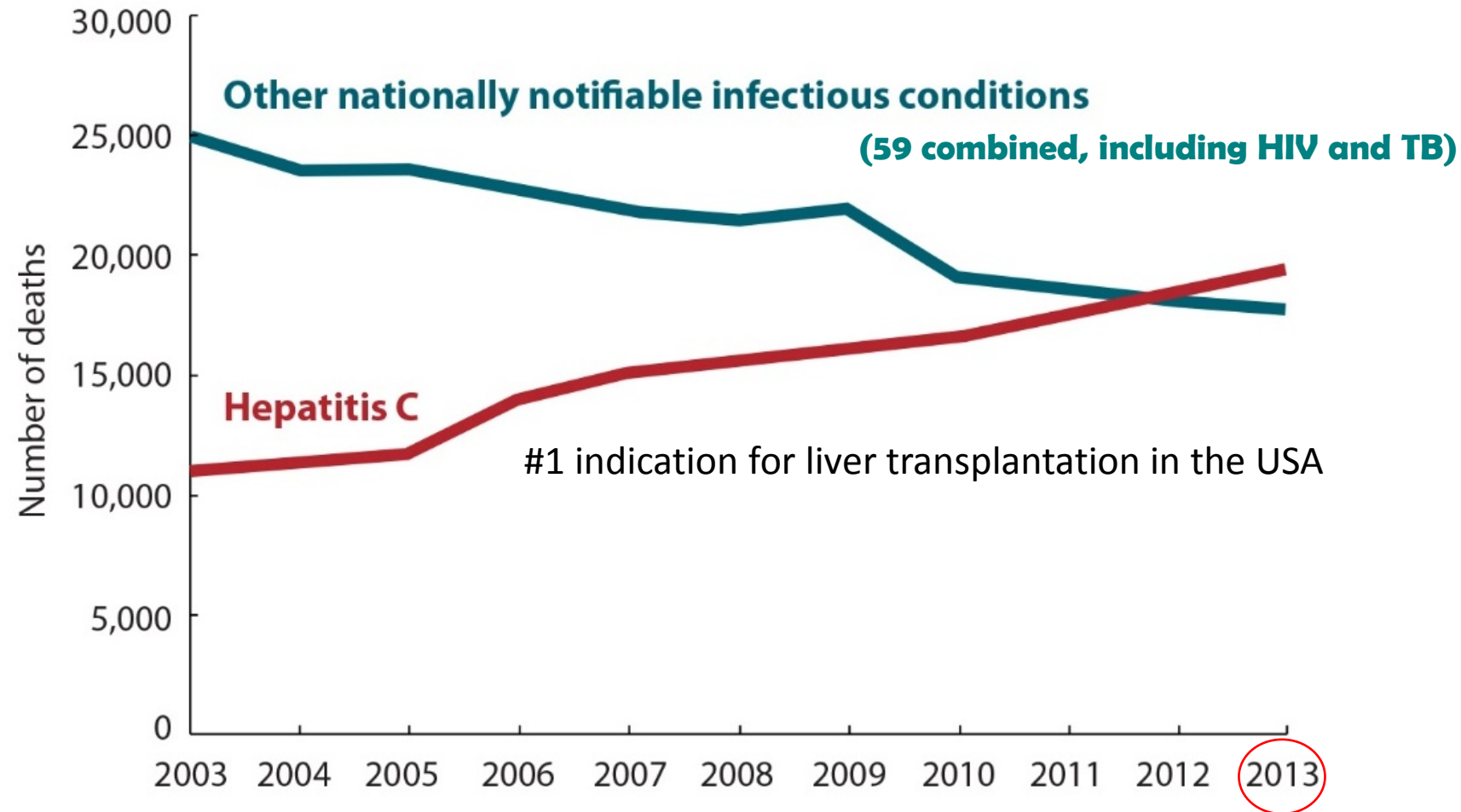
M. Carrington (Harvard)

# Individuals who spontaneously clear HCV have distinct genetic markers



Duggal P, et al.  
*Ann Intern Med* 2013

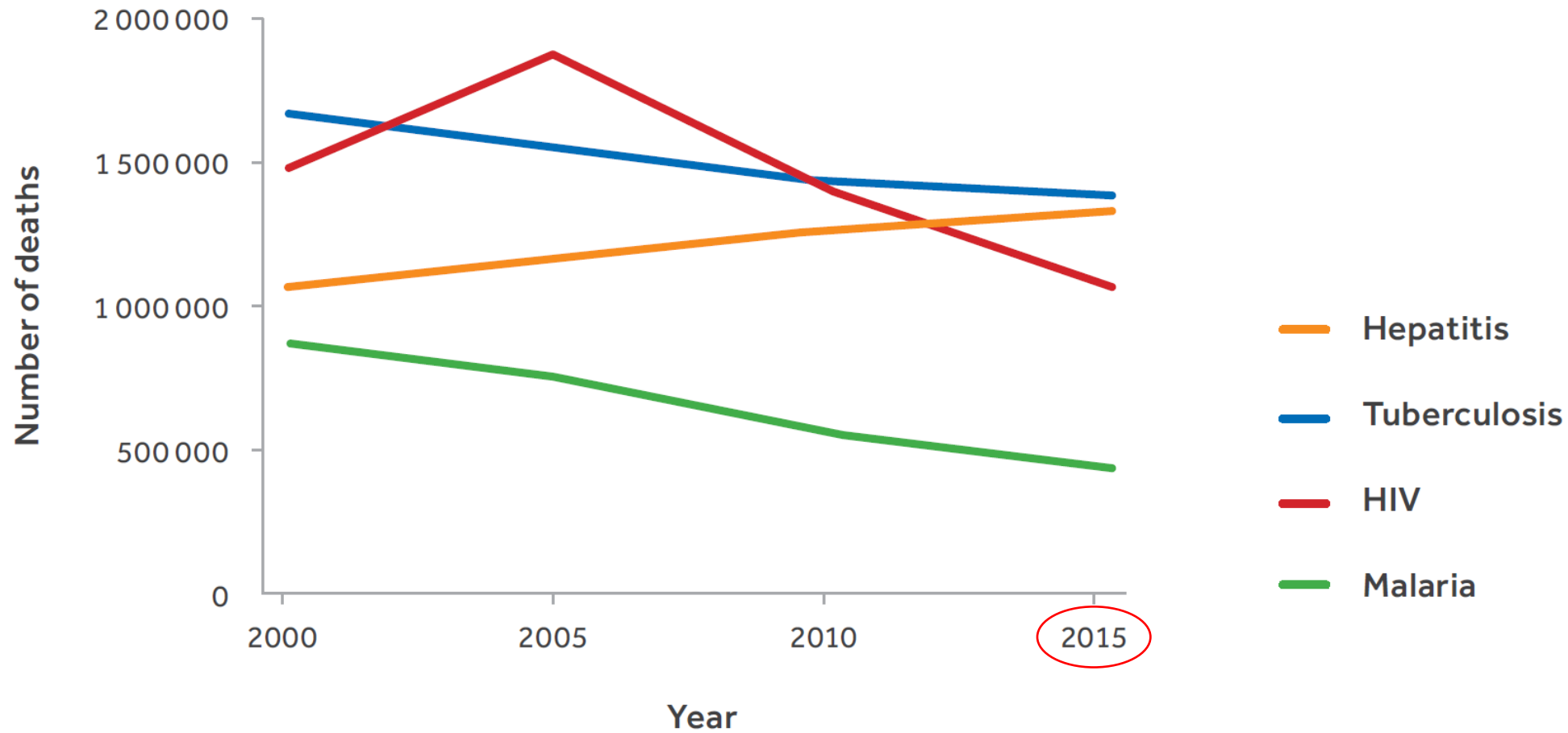
# CDC: Hepatitis C kills more Americans than any other infectious disease



Source: Centers for Disease Control and Prevention

<https://www.cdc.gov/nchhstp/newsroom/2016/hcv-mortality.html>

# Hepatitis is also a Global Killer



Source: WHO global health estimates (Global Health Estimates 2015: deaths by cause, age, sex, by country and by region, 2000-2015. Geneva: World Health Organization; 2016.)

# NCI Report to the Nation on the Status of Cancer

Cronin KA, et al. *Cancer* 2018 May 22

## *emphasis added*

- [Results] “***Liver cancer*** replaced thyroid cancer as the most rapidly ***increasing incident cancer*** among women.”
- [Discussion] “The ***largest increases in incidence*** rates were observed for ***liver cancer***, myeloma, melanoma of the skin, thyroid cancer, and leukemia.”
- [Discussion] “Overall cancer death rates have continued to decrease among both men and women for all major racial and ethnic groups, ... In contrast, ***cancer death rates increased for liver***, pancreas, and brain and other nervous system among men and women”
- [Discussion] “The ***increase in liver cancer death rates*** has been associated with the high prevalence of ***hepatitis C virus*** infection among Baby Boomers caused by...”

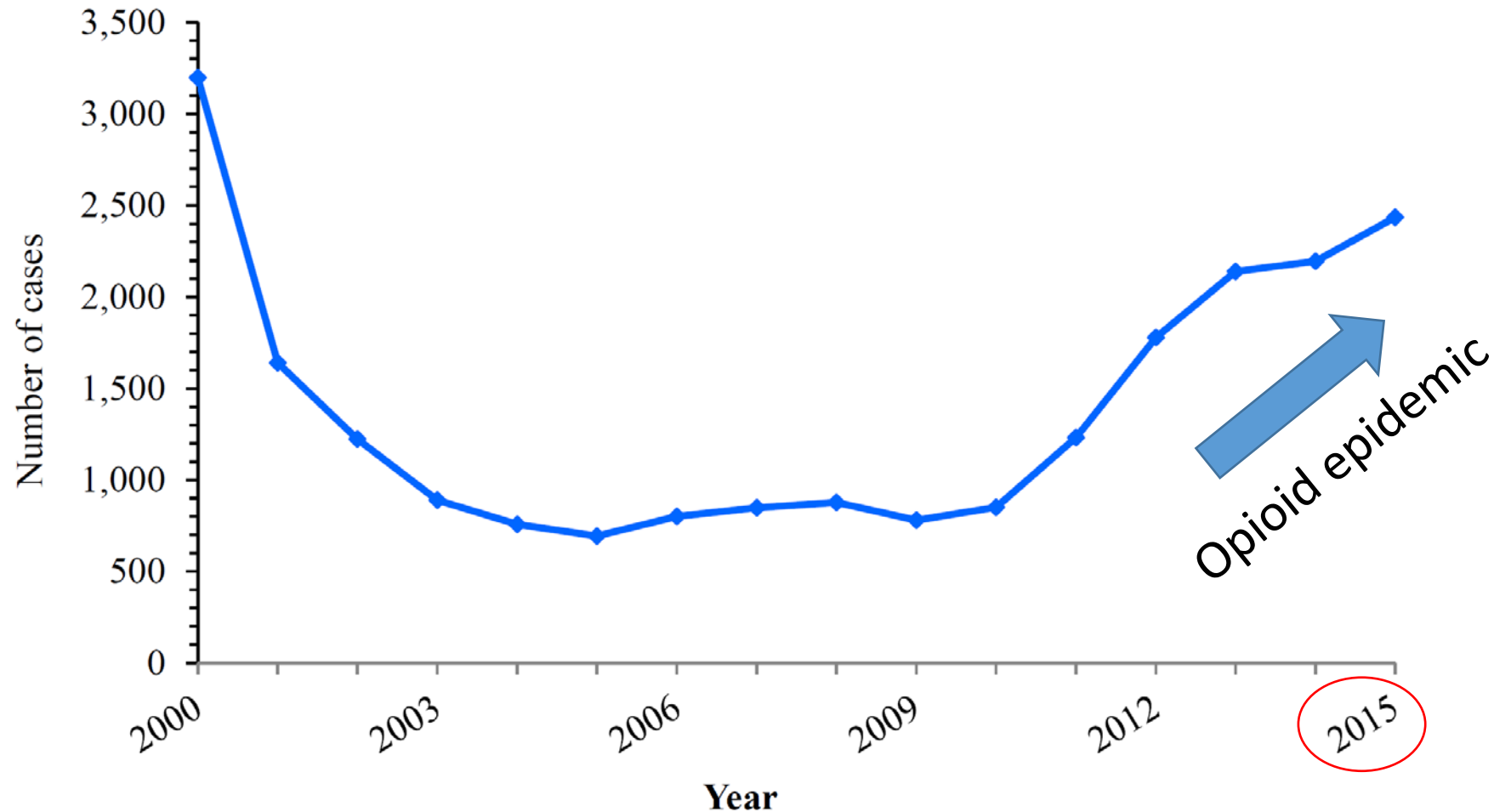


# HCC in HCV

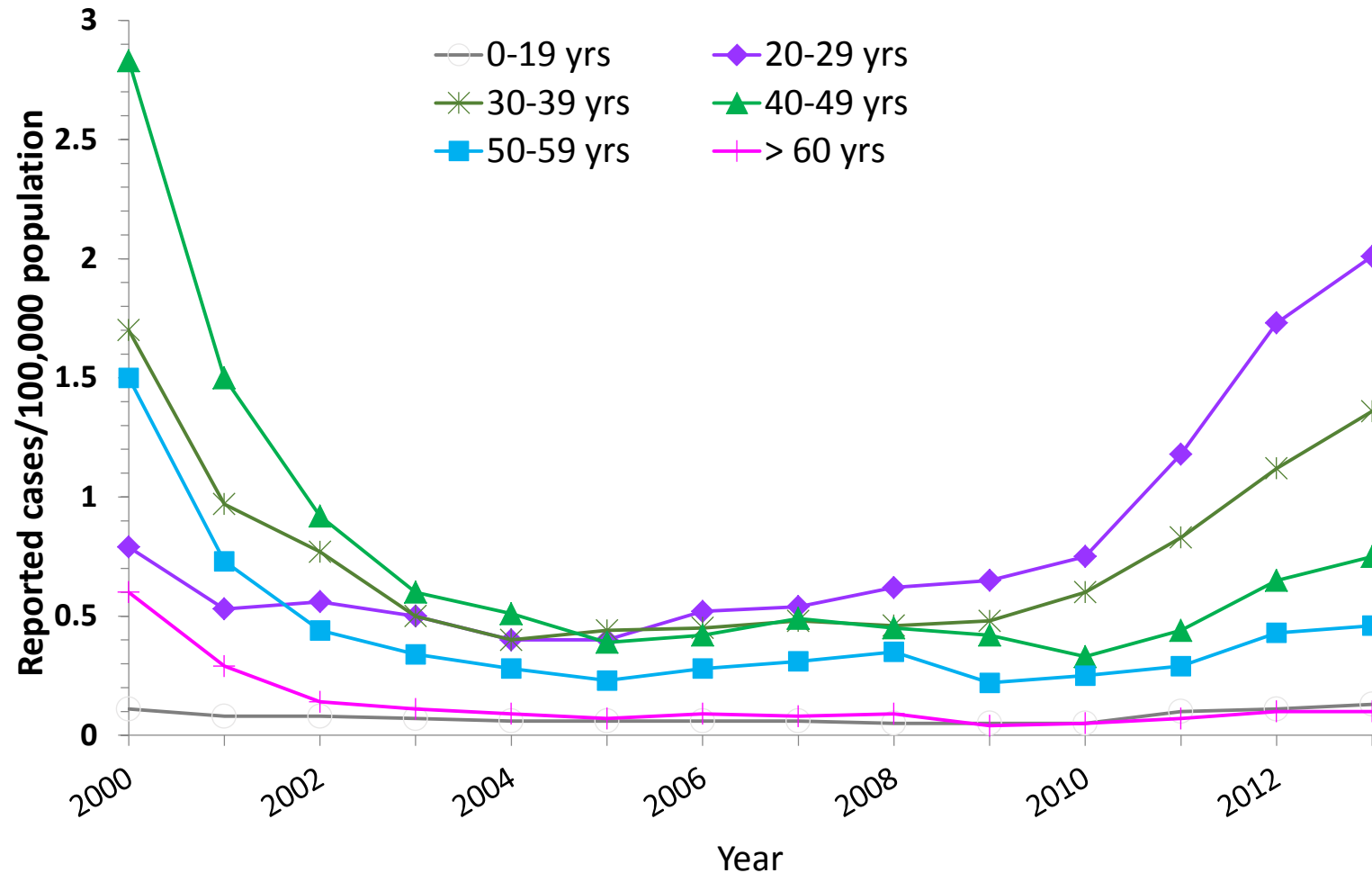
- HCV is a major cause of liver disease resulting in HCC
- Unlike for HBV, HCV-related HCC is very uncommon prior to development of cirrhosis
- Chronic inflammation may drive HCC, and free radical generation may play an important role
- HIV may enhance risk of HCV-related HCC
- Risk of HCC is not eliminated after SVR

# Rising Incidence (new cases) of Hepatitis C

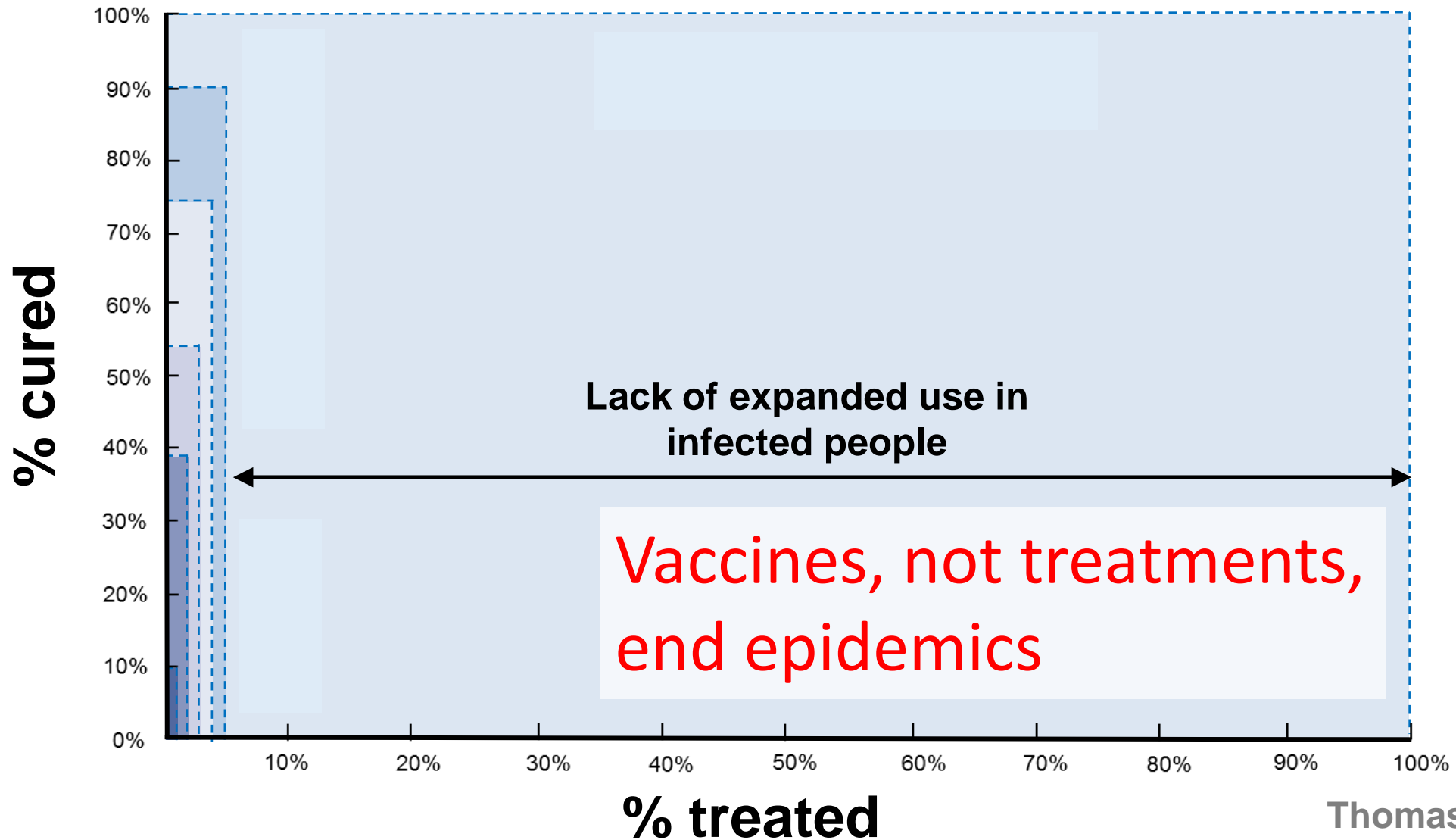
A predictable consequence of the opioid epidemic



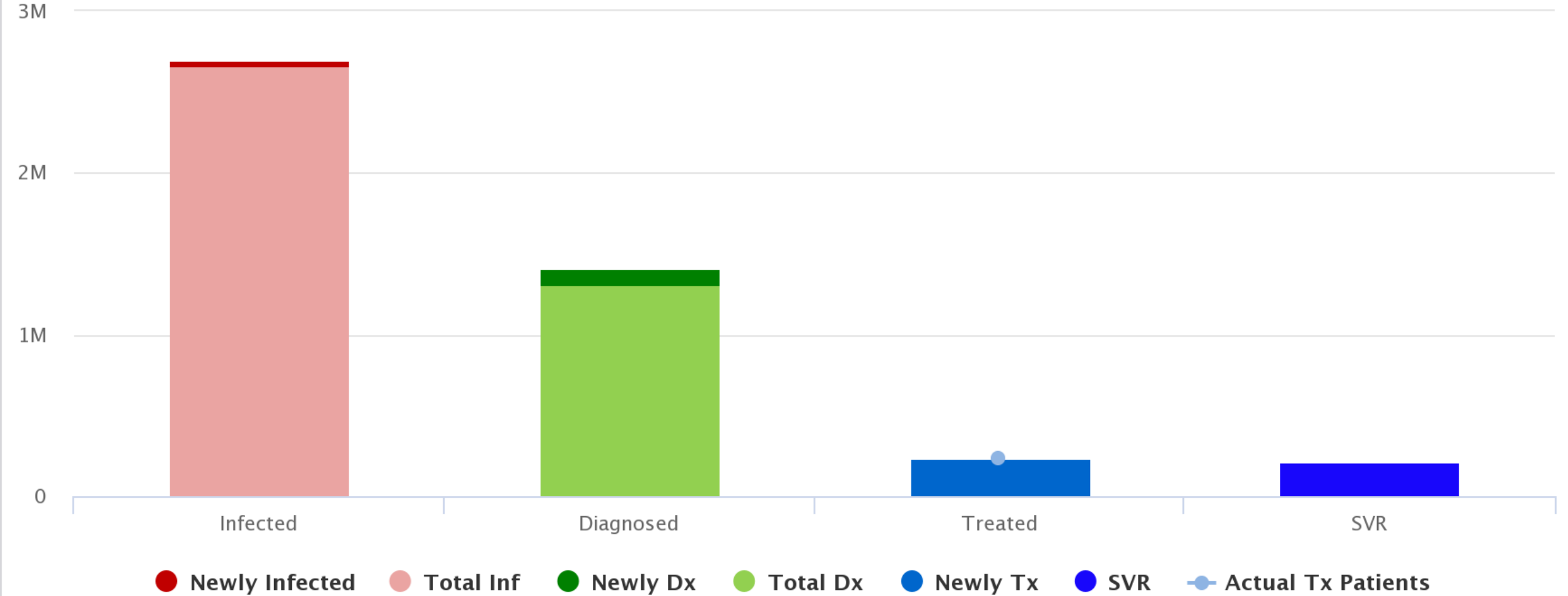
# Increasing incidence of acute HCV infection USA, 2000-2013



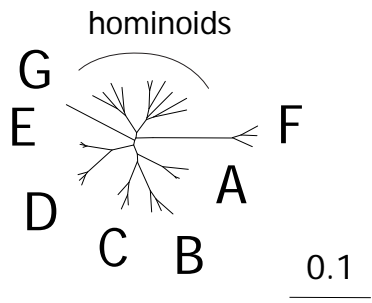
# Vast majority of HCV-infected individuals not treated: 3+ million in USA; 71 million worldwide



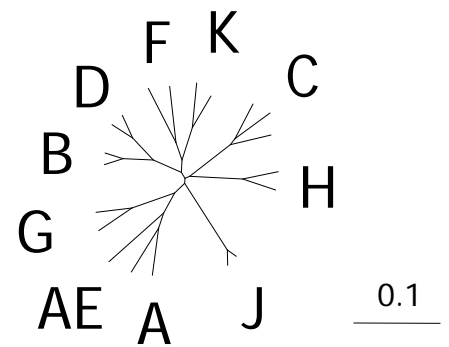
# Tx Cascade (USA, 2016 data set)



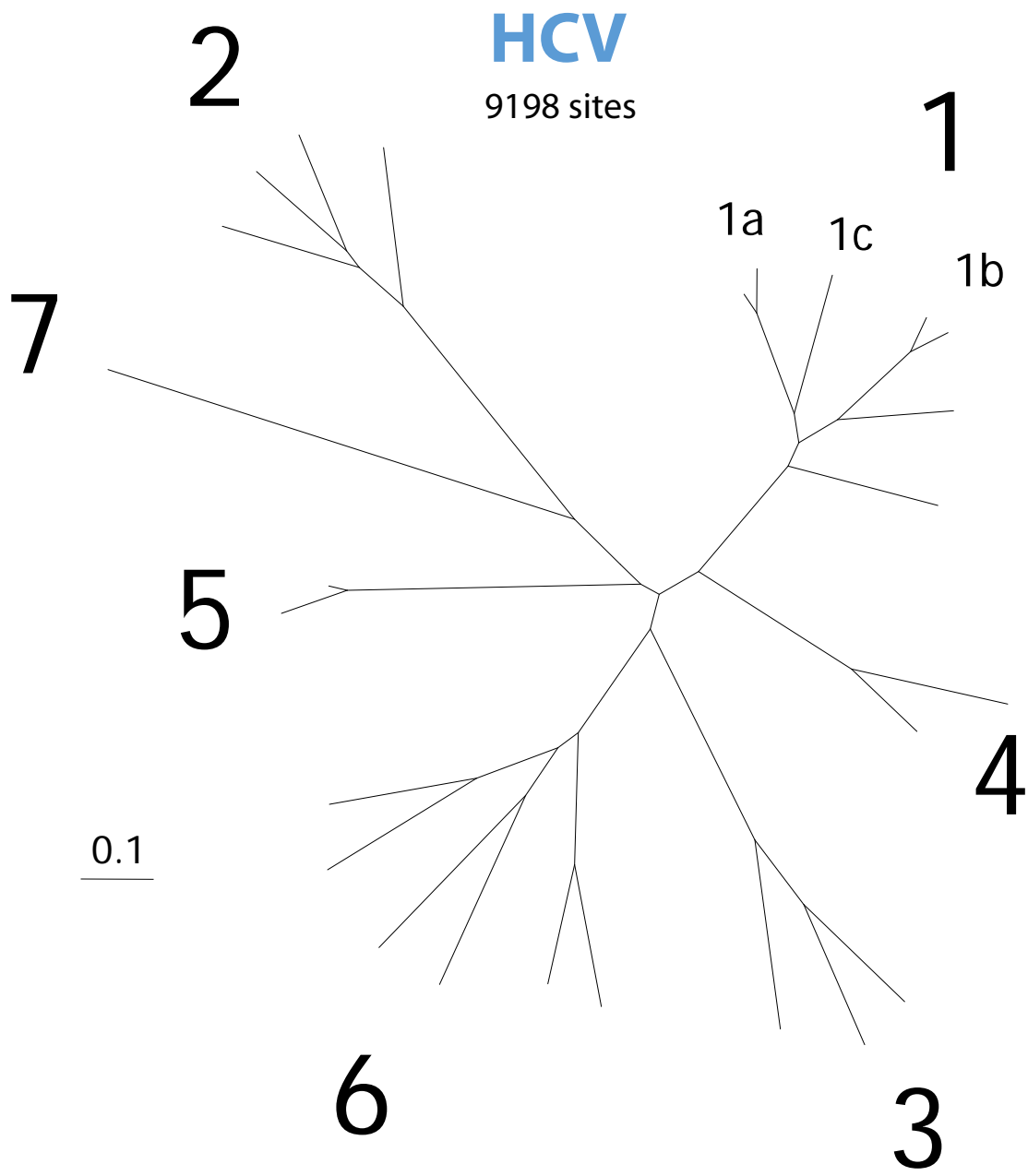
# Viral Genomic Diversity




**HBV**  
3181 sites



**HIV**  
8316 sites



 Irish HCV Outbreak (18 years)  
Ray *JEM* 2005

# Why expect that a HCV vaccine could work?

- 25% of natural infections resolve spontaneously
  - Micallef JM, et al. *J Viral Hepat* 2006; 13:34-41
- Protection against reinfection, even across genotypes
  - Mehta SH, et al. *Lancet* 2002; 359:1478-83
  - Lanford RE, et al. *J Virol* 2004; 78:1575-81
  - Osburn WO, et al. *Gastroenterology* 2010; 138:315-24
  - Sacks-Davis R, et al. *J Infect Dis* 2015; 212:1407-19
- Vaccine candidate that elicits strong anti-HCV T cell responses in humans
  - Barnes E, et al. *Sci Transl Med* 2012; 4:115ra111

# HCV Key Characteristics

## Viral vulnerabilities

- No non-human reservoir
- Inefficient transmission
- No nuclear archive
- No stable sanctuary
- Curative therapy

## Assets for the virus

- Replicative fecundity
- Genetic plasticity
- Stealth
- High prevalence
- Reinfection after cure



# Ending the HCV Pandemic, and attendant HCC

- No infectious disease has ever been controlled on a global scale by treatment
  - Notable failures: TB, syphilis, gonorrhea, chlamydia
- Vaccines are the greatest success story in biomedicine with incalculable benefits
  - Smallpox, HBV, HPV, HiB, ...