Global Under Diagnosis of Viral Hepatitis

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Research contracts/grants

- Roche
- Siemens
- Merck
- Hologic (Gen-Probe)
- Boehringer Ingelheim

- Honoraria are donated to BCCDC Foundation for Population & Public Health
- No gifts
half-full
not full enough
Objectives

1. Review global HCV epidemiology
2. Highlight gaps with traditional surveillance
3. Introduce molecular epidemiology
4. Suggest that an arranged marriage between traditional surveillance and molecular epidemiology might be a solution to better assess the global HCV disease burden
Population Burden of HCV at any Point in Time

Number of new infections “incidence” (adjustment spontaneous clearance)

Number cured (uptake & effectiveness)

Mortality (acquisition risks, viral sequelae co-morbid conditions, age)

Homie Razavi et al.
Current transmitters PWID

Bridging transmitters MSM/Sex trade

Low transmission risk
• Baby boomers/immigrants

Developed World

High
Moderate

General population

Developing World

High
Moderate

unsafe needle practices +/- unscreened blood products

higher transmission risk
Global epidemiology of HCV infection: Estimates of age-specific antibody to HCV seroprevalence ≈ 185 M (2.8% (95% CI: 2.6%-3.1%))

~25% will clear spontaneously
≈ 138M viremic cases
Mortality adjustment?
Gower et al. (J Hepatol 2014) - reported adjustments + extrapolated estimates

• Global anti-HCV prevalence of 1.6% (1.3% - 2.1%)

• 104 M (87-124 M) were adults (> 15 yrs old), 2.0% (1.7 - 2.3%) were Ab positive

• 80 M (64 – 103 M) people were RNA positive, 1.1% (0.9 - 1.4) viremic, most were adults
HCV Viremic Infections
(Prevalence & Total Infected)

Hepatitis C disease burden and strategies to manage the burden

Dore et al. J Viral Hepatitis 2014
Countries Responsible for 80% of Total Viremic HCV Global Infections

Optimize population level outcomes:

- ↓ Transmission – single use needles/syringes, an infection control framework; *Treatment as Prevention*?+ harm reduction
- Treat baby boomer/age cohorts which differ by country

Understand:

- Local transmission dynamics → driving incidence
  - Triage process → prioritize Rx to those most in need
    - Affordability or capacity perspective?
    - Avert existing health costs (~liver related)
- Follow up with broader Rx → elimination
• Molecular epidemiology can characterize the transmission history of an epidemic
• Genetic diversity of HCV and transmissions unfold at the same time
• People with similar sequences → represent transmission clusters

• Quasispecies → replication
• Host immune response
• Viral fitness
• Different hosts
• Genomic region interrogated
• Technology – Sanger/NGS

- NeT using genetic data (Bayesian skyline plot) versus N (estimated from surveillance data using back calculation)
- Plots truncated after 1990 - to characterize HCV transmission prior the virus' discovery in 1989
Sept 21, 2014: tested 1,380,020 individuals; 75,937 anti-HCV+; includes 9,106 seroconverters:
- 1st-time Ab positives, unknown infection duration
- Past seroconverters, est. infection duration >1 year
- Recent seroconverters in 2011

Sanger Sequenced

- RNA extractions from Serum (n=1540)
- Detected HCV RNA (>200 IU/ml) (n=1138)
- Total samples sequenced (n= 647)

- NS5B 650 bp sequence (n= 593)
- Core-HVR1 920 bp sequence (n= 415)
- HVR1 100 bp sequence (n= 466)

Olmstead, submitted
NS5B Clusters

- Common cluster
- Genotype 1a
- Genotype 3a
- Genotype 2b
Transmission Clusters

63 (11%; lower cutoff) and 92 (15%; higher cutoffs) individuals were identified in NS5b clusters

- No clusters between BC and reference sequences → baby boomers tended not to cluster → infected in the past

27 individuals in 13 clusters were identified in all three genomic regions

29 individuals identified in clusters, were first-time positives
Those in clusters had an increased likelihood of having estimated duration of infection < 1 year (compared to 1st time pos) OR 3.19 (95% CI, 2.03 – 5.03)

Were more likely to be genotype 1a, AOR 4.86 (95% CI, 1.44 - 30.35) and 3a infected, AOR 2.99 (95% CI, 0.95 – 23.97)

Were more likely to be < 40 yrs old (compared to those > 40 yrs old), AOR 1.95 (95% CI, 1.18- 3.24)
Differentiation of Acute from Chronic HCV Infection by NS5B Deep Sequencing

Deep sequence NS5B amplicons

Shannon Entropy diversity quantification

- 33%
- 22%
- 22%
- 11%
HCV NS5B Diversity Differentiates Acute from Chronic Infection

WD n = 39
AUC = 0.96

TD n = 94
AUC = 0.86
Systematic application of molecular epidemiology and integration with traditional surveillance could profoundly improve the accuracy of global HCV disease estimates – right investment in the developing world?

Baseline diagnostic sample
• Infection timing
• Assess number of individuals involved in transmission clusters → growing? or stable?
• NGS-based diversity measures → improve incidence and prevalence estimates
Population level tool

• Incident infections → target prevention resources
  • Iatrogenic transmission elimination
  • Treatment as Prevention?

• Prevalent infection → Rx of aging cohorts/baby boomers

• Serum fibrosis marker testing → liver disease triage → help identify those needing urgent Rx – developing world?