Across borders:
The challenge of HBV & HCV with increasing globalization

Prof CL Lai
University of Hong Kong
Hong Kong
Disclosure

• I am personally responsible for this…
Overview

- Introduction: HBV & HCV
- Global burden
  - Effects of migration from high to low incidence countries
  - Effects of HBsAg escape mutants on vaccination
  - Challenges to “elimination” of hepatitis by 2030
Introduction: HBV & HCV
Introduction: HBV & HCV

HCV

- RNA virus
- Replication entirely cytoplasmic
- Resides only in the liver
- Transmission: parental only, mainly through transfusion or intravenous drug use
- Most hepatocellular carcinoma (HCC) due to underlying cirrhosis
- >95% cure with 8–12 weeks of DAAs
Introduction: HBV & HCV

HBV

- Double-stranded DNA virus with integration into host DNA
- Extra-hepatic pool, e.g. lymphocytes, testis
- Oncogenic virus (gene X, pre-S1,2); ~20% HCC non-cirrhotic
- Transmission: parental only, mostly at birth or in early childhood, also unsafe sex
- Currently “functional” cure with loss of HBsAg only in ~10%; the rest requires long-term treatment
HBV & HCV global burden/incidence
**HBV vs HCV (2015)**

**Global Incidence**
- **HBV**: 257 million
- **HCV**: 71 million

**Distribution**
- **HBV**: Highest: Africa, W Pacific
- **HCV**: Highest: Middle East

*WHO Global Hepatitis Report 2017.*
HBV: Incidence in children <5 years old


% HBsAg+ in Children <5 yrs

- 3.0
- 0.2
- 1.6
- 0.4
- 0.7
- 0.9

The Hong Kong Association for the Study of Liver Diseases
HCV: Incidence


The Hong Kong Association for the Study of Liver Diseases

Incidence/100,000

- 31.0
- 6.4
- 62.5
- 61.8
- 14.8
- 6.0
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* Rate lower with younger age

Question

With HBV infection, what is the chance of chronicity for adults acquiring acute HBV infection?

1. 50-80%
2. 10-20%
3. <3%
Infection acquired at adolescence and adulthood

Chronicity rate from different studies

- US veterans 0.26% (n = 579)\(^1\)
- Greece 0% (n = 189)\(^2\)
- Greece 0.2% (n = 507)\(^3\)
- Sweden 0% (n = 100)\(^4\)
- Japan 1% (n = 301)\(^5\)

\(^1\)NEJM 1987; 316:965;
\(^2\)Infection 1985; 13:174;
\(^3\)Gastroenterology 1987; 92:1844;
\(^4\)Eur J Clin Microbiol Infection Dis 2000; 19:21;
\(^5\)Hepatology 2006; 44:326.
## HBV vs HCV (2015)

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<td><strong>Co-infection with HIV</strong></td>
<td>~2.7 million</td>
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<td><strong>New infections</strong></td>
<td>Declining because of vaccination</td>
<td>Increasing because of unsafe injections</td>
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<td><strong>Current treatment</strong></td>
<td>Long-term/life-long</td>
<td>8–12 weeks only</td>
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*WHO Global Hepatitis Report 2017.*
# Hepatitis virus-related mortality data (2015)

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<td><strong>Cirrhosis</strong></td>
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<td>462,690</td>
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**Total deaths by viral hepatitis 1.34 million**

Global annual mortality 2000-2015 (WHO health estimates)

No. of Deaths

Year


Mortality from viral hepatitis up by 22% since 2000

- 1.1 million deaths in 2000
- 1.34 million deaths in 2015

Effects of migration
HBV

The high incidence areas

• For adults: China, South East Asia and Africa

• For children <5 yrs old: Africa and Eastern Mediterranean

Migration to low incidence areas

• Mainly affects the migrant groups only;
  little effect on the host country

• 2 examples:
First example: HBV & HCV in Belgium

460 Chinese immigrants screened

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<td>50–80</td>
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HBV & HCV in Belgium

460 Chinese immigrants screened

• Results available from 456 persons

• Anti-HCV positive: 0

• HBsAg positive: 32/456 (7%)
  - 19/32 (59.4%) unaware of their HBV infection

• Anti-HBc positive: 244/456 (53.5%)

Second example: migrants from China to Hong Kong

Recent epidemiological study in HK

- 2015–2016: n = 10,256
- HBsAg positive: 7.8%
- Vaccine vs no vaccine: 3.4% vs 8.3% (p<0.01)
- Vaccination group:
  - HK born vs Mainland China born 1.8% vs 9% (p<0.001)

Liu K et al. (J Infect Dis 2019 in press)
HBV

Migration to low incidence areas

• Effect on the host population minimal because chronicity in adult infection is low

• Example: IVDUs
  - new infection: HBV 1% vs HCV 23%
  - chronic infection: HBV 0.5% vs HCV 8%

HBV

Migration of people from high incidence countries to low incidence countries

• Risk of transmission to host country very low
• Would increase the burden of care for the infected immigrants (to be discussed later)
• The care/lack of care for the infected immigrants themselves should remain the same, but may actually be better
HCV

The high incidence areas

• Eastern Mediterranean and Europe

Migration to low incidence areas (starting with colonization and the slave trade!)¹

• Dissemination of different genotypes

Possible route of HCV integration worldwide

HCV integration and migration

Example of intra- and trans-continental spread

HCV genotype 4 *intra-continental* spread

- First identified in Egypt with treatment of Schistosomiasis
- Now continues to occur with inadequate sterilization of medical instruments, also through non-medical sources like scarification, circumcision
- Intra-continental spread to Sudan, Zaire, Cameroon etc. through scarification, circumcision, sex

HCV integration and migration

Example of intra- and trans-continental spread

HCV genotype 4 trans-continental spread

- Trans-continental spread to Europe, especially the Mediterranean countries: Italy, France, Greece, and Spain, where 10–24% of HCV are G4\(^1,2\)

- Most frequently among IVDUs; also through organ transplant, transfusion\(^3,4\)

HCV

Migration of people from high incidence countries to low incidence countries

• Risk of transmission to host country of rare genotypes high especially among IVDUs

• Would increase the burden of care for the infected immigrants (to be discussed later)

• The care/lack of care for the infected immigrants themselves should remain the same, but may actually be better
HBsAg escape mutants and their effects on vaccination
Question 2

Is the HBsAg escape mutant a threat to global vaccination efficacy?

1. Yes
2. No
HBsAg escape mutants

• First reported in 1990 in Italy, with mutation in aa 145 (sG145R)\(^1\)

• Chronic infections with sG145R mainly present in
  - infants born before institution of HBIG and vaccine
  - infants with vaccine failure. They become infected by
    the mutant virus either *in utero* or through selection by
    the passive immunity of HBIG
  - may result in false negative HBsAg testing (frequency unknown)

HBsAg escape mutants

• There was NO increase in s-escape mutants after universal vaccination

• The yeast recombinant vaccine is protective against both wild type and mutant virus

The global goal of HBV & HCV elimination by 2030
HBV & HCV elimination by 2030

Problems to overcome

• Prevention of new infections

• For the existing chronic carriers
  - identification of cases
  - access to testing
  - reluctance to seek medical advice
  - access to treatment
  - patient compliance
  - sustainability
Question 3

According to your personal opinion, which of these 6 problems are likely to be persistent even in 2030?

1. Identification of cases
2. Access to testing
3. Reluctance to seek medical advice
4. Access to treatment
5. Patient compliance
6. Sustainability
HBV & HCV elimination by 2030

Problems to overcome

• Prevention of new infections

• For the existing chronic carriers
  * - identification of cases
  * - access to testing
  * - reluctance to seek medical advice
  * - access to treatment
  * - patient compliance
  * - sustainability

* Personal opinion: Likely to remain persistent problems!
Prevention of new HBV infections

HBV: a great success story

- Global coverage of HBV vaccination by 2015 ~84%
- Incidence in children <5 decreased from 4.7% to 1.3%
- Best coverage areas W Pacific region and the Americas: 70–80%
- Worst coverage Africa ~10%

HBV 5 Year Old Prevalence Elimination Targets
2017

http://cdafound.org/polaris. 2018
Prevention of new HBV infections

The reasons babies are still infected despite vaccination program

- Timing of the birth dose of HBIG
- Delivery of the 3 doses of vaccines
- High maternal HBV DNA load >10^6–8 IU/mL
- Now remediable with prompt treatment in the last trimester of these mothers with tenofovir (currently only TDF approved). Dependent on health care provisions and compliance of carriers
Prevention of new HBV infections

HBV: a great success story

The USA as an example of success

Stepwise gradual decline of acute HBV from 26,116 cases (1985) to ~3000 (2010–2015):

1. Vaccination of HBsAg positive mothers
2. Testing of all pregnant women
3. Universal vaccination of all babies
4. Vaccination of children 0–18 yrs old

AND

5. Change in risk behaviors (benefit from HIV control)

Prevention of new HBV infections

The USA as an example of success

Report from National Health and Nutrition Examination Survey (NHANES)

• Stable HBsAg prevalence of 0.3–0.4% since 1988

• Largely due to Asian Hispanic immigrants with incidence of 3.1%

• Decline of prevalence among 6–19 yrs old
  - 0.2% (1998–1994) to 0.03% (2007–2012)

HCV Elimination Targets 2017

On Track  Working Towards  Not On Track

http://cdafound.org/polaris. 2018
Prevention of new HCV infections

Transmission persists!!

• Compared to the second half of the 20\textsuperscript{th} century, several countries reported lower incidence of HCV in historical epidemiology studies\textsuperscript{1,2,3}

• WHO reports 1.75 million \textit{new} infections in 2015 (incidence rate 23.7 per 100,000), exceeding the number being treated\textsuperscript{4}

Prevention of new HCV infections

Transmission persists!!

- Main routes
  - IV drug use: accounts for 23% of new HCV infections
  - unsafe health care practices
    - distribution of syringes for IVDUs 27/person/year (instead of the target 200/year)
      [ ZERO syringes in the HK Methadone Clinics!!]
    - in low-income countries, 34% donated blood not screened with basic quality procedures
    - in 2010, 5% injection with unsterilized, reused devices
    - 4% in E Mediterranean and 5% in SE Asia regions!!

*WHO Global Hepatitis Report 2017.*
The existing HBV & HCV carriers
The 3 public health issues

1. Access to testing
   • Rapid tests including dried blood spot, oral fluids
   • Who to test?
     - where incidence is ≥2% or ≥5%, all adults\(^1\)
     - HBV: family members, sex partners
     - HCV: IVDUs
     - Funding??

The 3 public health issues

2. Access to treatment – HBV

Highly variable in different countries

- USA and Canada: based on income & insurance
- Taiwan: 3 years of antiviral only
- China: for those with state insurance
- HK lifelong free treatment
The 3 public health issues

2. Access to treatment – HCV

HCV with the 8–12 weeks of DAA treatment

• Even more variable in different countries
  - Canada: free treatment including prisoners
  - USA: based on income & insurance
  - Taiwan: only for IFN+ ribavirin failures with F3
  - China: for those with state insurance 60% reimbursement
  - HK: only for patients with F3 (prisoners not included)
  - Thailand: for patients with F2 (prisoners can apply!)
The 3 public health issues

2. Access to treatment

"The number of low- and middle-income countries with a scaled-up response is limited…Global fund to fight AIDS, TB and malaria does not provide for viral hepatitis”

The 3 public health issues

3. Sustainability of funding
   - Reducing the price of diagnostics and drugs
   - Global funding?
The 3 most difficult problems
1. Identification of cases

- According to WHO Global Report 2017, only 9% of the 257 millions of HBV carriers and 20% of the 71 millions of HCV carriers know their Dx

- The estimations of global carrier rates are dependent on population surveys. Data often obtained through extrapolation. Under-estimations are to be expected
The 3 Most Difficult Problems

2. Reluctance to seek medical advice

• What are the percentages of known carriers who have sought medical advice and have preliminary blood tests?

• This applies also to non-high risk groups. HBV and HCV carriage are asymptomatic until the late stages.
The 3 Most Difficult Problems

3. Patient compliance

- Drug compliance, currently HBV antivirals for life (and HCV DAAs 8–12 weeks), need strong doctor-patient relationship, which may be difficult especially in low income countries

- Compliance to life-long 6 monthly ultrasonography
Conclusions
Conclusions

Global incidence

New infections

Effects of migration

Prevention of new infections

HBV

257 million

Declining because of vaccination

Effect on the host population minimal

Incidence in children <5 now 1.3%

HCV

71 million

Increasing because of unsafe injections

Transmission of rare genotypes

1.75 million new infections (2015): IVDUs, re-used syringes
Conclusions

• Problems with existing carriers common for both HBV & HCV
  - identification of cases
  - reluctance to seek medical advice
  - patient compliance
  - access to testing
  - access to treatment
  - sustainability

  Likely to be persistent
  Dependent on country & global efforts
Elimination of HBV & HCV 2030

And the blots of Nature’s hand

Shall not in their issue stand!

W Shakespeare:  
A Midsummer Night’s Dream
Thank you!
And Happy 2019!!