Hepatitis C epidemiology

- 3% of world population infected
- >170 million chronic carriers world-wide
- > 30 million cases in SEAR
- ~ 60 million cases in WPR
- appears to be spreading
- 3.9 million cases in the USA
- 50'000 new cases annually in the USA
  - 8’000 deaths/year > double in 10-20 years
Viral Hepatitis Burden

- 350 million chronic carriers of hepatitis B
  - 1’200’000 annual deaths

- 170 million chronic carriers of hepatitis C
  - 500’000 annual deaths?
# Viral Hepatitis Prevalence & Mortality

<table>
<thead>
<tr>
<th></th>
<th>hepatitis C</th>
<th>hepatitis B</th>
<th>HIV/AIDS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>global prevalence</strong></td>
<td>3%</td>
<td>35%</td>
<td>0.50%</td>
</tr>
<tr>
<td></td>
<td>170 million</td>
<td>1.2 billion</td>
<td>36.1 m</td>
</tr>
<tr>
<td><strong>chronic infection</strong></td>
<td>2.30%</td>
<td>6%</td>
<td>0.50%</td>
</tr>
<tr>
<td></td>
<td>129 million</td>
<td>350 million</td>
<td>36.1 m</td>
</tr>
<tr>
<td><strong>deaths per year</strong></td>
<td>476 000</td>
<td>1.2 million</td>
<td>2.8 million</td>
</tr>
<tr>
<td><strong>annual death rate</strong></td>
<td>0.40%</td>
<td>0.49%</td>
<td>7.80%</td>
</tr>
<tr>
<td><strong>lethality</strong></td>
<td>7-10 %</td>
<td></td>
<td>~100 %</td>
</tr>
</tbody>
</table>
Hepatitis C: public health aspects

- Prevalence
- Incidence
- Patho-physiological implications
- Socio-economic burden
- Management
<table>
<thead>
<tr>
<th>Region</th>
<th>Population (millions)</th>
<th>Chronic infections (millions)</th>
<th>HIV</th>
<th>HCV</th>
<th>HBV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>749</td>
<td>22.7</td>
<td>22.5</td>
<td>59.3</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>3,585</td>
<td>7.3</td>
<td>107.5</td>
<td>286.8</td>
<td></td>
</tr>
<tr>
<td>Latin America</td>
<td>504</td>
<td>1.7</td>
<td>15.1</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>729</td>
<td>0.8</td>
<td>21.8</td>
<td>10.9</td>
<td></td>
</tr>
<tr>
<td>Oceania</td>
<td>30</td>
<td>0.0</td>
<td>0.9</td>
<td>2.4</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>305</td>
<td>0.9</td>
<td>9.1</td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>5,902</strong></td>
<td><strong>33.4</strong></td>
<td><strong>176.9</strong></td>
<td><strong>371.6</strong></td>
<td></td>
</tr>
</tbody>
</table>

UNAIDS, WHO
HCV prevalence

prevalence for each country was estimated based on the following criteria (1):

- one representative percentage country
- studies on the healthy general population
- largest well selected population sample
- community-based studies if available
- several ethnic groups represented
HCV prevalence

Prevalence for each country was estimated based on the following criteria (2):

- several regions represented
- all ages represented
- good balance between sexes
- use of 2nd or 3rd generation HCV tests
- well designed study
<table>
<thead>
<tr>
<th>COUNTRY</th>
<th>%HCV</th>
<th>COUNTRY</th>
<th>%HCV</th>
<th>COUNTRY</th>
<th>%HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Austria</td>
<td>0.21</td>
<td>Greece</td>
<td>1.51</td>
<td>Portugal</td>
<td>0.46</td>
</tr>
<tr>
<td>Belarus</td>
<td>1.44</td>
<td>Hungary</td>
<td>0.98</td>
<td>Romania</td>
<td>4.50</td>
</tr>
<tr>
<td>Belgium</td>
<td>0.87</td>
<td>Iceland</td>
<td>0.06</td>
<td>Russia</td>
<td>2.00</td>
</tr>
<tr>
<td>Bulgaria</td>
<td>1.11</td>
<td>Ireland</td>
<td>0.10</td>
<td>Slovak Republic</td>
<td>0.39</td>
</tr>
<tr>
<td>Croatia</td>
<td>1.40</td>
<td>Israel</td>
<td>0.44</td>
<td>Spain</td>
<td>0.74</td>
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<tr>
<td>Cyprus</td>
<td>0.10</td>
<td>Italy</td>
<td>0.48</td>
<td>Sweden</td>
<td>0.00</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>0.24</td>
<td>Luxembourg</td>
<td>0.50</td>
<td>Switzerland</td>
<td>0.24</td>
</tr>
<tr>
<td>Denmark</td>
<td>0.25</td>
<td>Moldova</td>
<td>4.90</td>
<td>Turkey</td>
<td>1.50</td>
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<tr>
<td>Finland</td>
<td>0.02</td>
<td>Netherlands</td>
<td>0.10</td>
<td>Ukraine</td>
<td>1.20</td>
</tr>
<tr>
<td>France</td>
<td>1.15</td>
<td>Norway</td>
<td>0.09</td>
<td>United Kingdom</td>
<td>0.02</td>
</tr>
<tr>
<td>Germany</td>
<td>0.12</td>
<td>Poland</td>
<td>1.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>country</td>
<td>prevalence</td>
<td>deaths/year</td>
<td>mortality/100,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>------------</td>
<td>------------</td>
<td>-------------</td>
<td>-------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Austria</td>
<td>0.21</td>
<td>70</td>
<td>1.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bangladesh</td>
<td>2.4</td>
<td>11,500</td>
<td>9.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bolivia</td>
<td>16.3</td>
<td>4,900</td>
<td>65.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brazil</td>
<td>2.6</td>
<td>16,700</td>
<td>10.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Canada</td>
<td>0.15</td>
<td>180</td>
<td>1.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chad</td>
<td>4.8</td>
<td>1250</td>
<td>19.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>China</td>
<td>4.07</td>
<td>231,600</td>
<td>18.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>18.1</td>
<td>45,800</td>
<td>72.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>0.84</td>
<td>1,900</td>
<td>3.1</td>
<td></td>
<td></td>
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<tr>
<td>France</td>
<td>1.15</td>
<td>2,600</td>
<td>4.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Germany</td>
<td>0.12</td>
<td>390</td>
<td>0.48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>1.85</td>
<td>69,900</td>
<td>7.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td>2.1</td>
<td>16,900</td>
<td>8.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Italy</td>
<td>0.48</td>
<td>1100</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japan</td>
<td>2.3</td>
<td>11,500</td>
<td>9.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nigeria</td>
<td>1.4</td>
<td>6,400</td>
<td>5.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Estimated Incidence of Acute Hepatitis C United States, 1982-1993

Source: CDC Sentinel Counties Study of Acute Viral Hepatitis
Hepatitis C: Genotypes

- extended endemic areas for subtypes:
  - West Africa (types 1 and 2)
  - West Central & Central Africa (type 4)
  - Indian subcontinent (type 3)
  - South East Asia (type 6)
  - Only type 5 no endemic area found

- important number = long history of endemic presence
- limited diversity = recent introduction (Canada, Australia, W-Europe)
Hepatitis C: Genotypes

*based on molecular rate of diversity, divergence dates:*

- more than 300 years back for subtypes
- more 500-2000 years for HCV types
  - may be an underestimate due to methodological limitations

*geographic distribution and genetic variation consistent:*

- global distribution of HCV
- long history that precedes by many centuries era of modern medicine
<table>
<thead>
<tr>
<th>Reported from</th>
<th>Hepatitis C prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>0.5%</td>
</tr>
<tr>
<td>Canada</td>
<td>0.6%</td>
</tr>
<tr>
<td>Japan</td>
<td>1.4%</td>
</tr>
<tr>
<td>Korea</td>
<td>0.6%</td>
</tr>
<tr>
<td>Egypt</td>
<td>11-19%</td>
</tr>
<tr>
<td>Australia</td>
<td>0.4%</td>
</tr>
</tbody>
</table>
New Viral Hepatitis Infections

New infections continue to occur:

- unscreened blood transfusions or blood products
- failure to sterilize medical equipment
- dental and “traditional” medicine
- injection drug users
New infections continue to occur:

- unsafe injections
- exposed health care workers
- hemodialysis

Rare high risk sexual practices, horizontal and perinatal transmission
Viral Hepatitis in Drug-Users

Seroprevalence

- HCV 43-98%
- HBV 45-86%
Hepatitis C: public health aspects

- Prevalence
- *Incidence*
- Patho-physiological implications
- Socio-economic burden
- Management
Estimated Number of Injection-Associated Infections with Bloodborne Pathogens Annually World-wide

- HBV infections: 8-16 millions
- HCV infections: 2.3 - 4.7 millions
- HIV Infections: 80,000 to 160,000

Kane et al, Bull WHO 1999
Screening for HCV Infection

In countries where resources and priorities allow, screening is recommended for:

- Persons who received transfusions or solid organ transplants prior to donor screening
- Persons who received plasma-derived products that were not virally inactivated
HCV Prevalence

- Whole population: 10-15%
- Rate gradient along Nile
  - High in Lower Egypt
  - Lower in Upper Egypt
  - Low in cities
- Genotype distribution:
  - Very homogeneous
  - Type 4 (a)
- Risk factors:
  - The typical risk factors
  - History of schistosomiasis
  - History of parenteral treatment against schistosomiasis

Frank et al, Lancet 2000
Research Questions:

Why does Egypt have such a comparatively high HCV prevalence?

Are there modes of potential HCV transmission unique to Egypt?

Can they account for current HCV prevalence?
Schistosomiasis lifecycle

- Snail habitat: irrigation canals, lakes, ponds
- Humans get infected through skin contact with water
- Rural population at high risk for
  - Infection
  - Chronic infection
  - Frequent re-infection
High schistosomiasis prevalence

- Nile was dammed to increase agricultural production starting ca. 1900
- Conversion to perennial irrigation using canals (multiple harvests)
- Aswan High Dam (1969) creating Lake Nasser, total cessation of Nile flood

- Population’s exposure to schistosomiasis increased, and prevalence rose strongly

Frank et al, Lancet 2000
Treatment of Schistosomiasis

- 1920s to 1980s: Parenteral anti-schistosomal therapy (PAT), course of multiple injections

- 1970s: oral treatment for *S. haematobium*

- 1982: oral treatment for *S. mansoni*
PAT in Endemic Disease Units

Year


No. of patients treated (x1000)

Intravenous PAT (with Tartar Emetic)
Intramuscular PAT (with Astiban)
Oral (with Metrifonate, Niridazole)

frank et al, lancet 2000
PAT Mass Treatment Scenario

“Patients are grouped according to weight and appropriate dose and are lined up in queues for admission in turn for injection....

The stranger to mass therapy with Tartar Emetic is certainly to be confounded by the speed and apparent safety of the administration of the drug. ...

The skilful doctor began injecting at 9.20 a.m. and completed 504 injections of men, women and children by 10.10 am. Allowing for a 10-minute rest, the time taken for each injection was thus just under 5 seconds. ...

This remarkable performance is being repeated at various tempos all over Egypt...”

Maegraith 1964 (witnessed 1962)
PAT Mass Treatment Scenario

“The used syringe is placed in an ‘out’ tray, from which it is taken by the Nurse, washed through and boiled for a minute or two. As soon as the syringe is cold, it is filled with a volume of the drug solution. ... It is then placed in the ‘in’ tray. ... There are usually 20 to 30 syringes in rotation.”

Maegraith 1964 (witnessed 1962)

Use of 20 to 30 syringes in rotation allows for a maximum of 1-2 minutes for handling and sterilization procedures...
## PAT’s special potential for HCV transmission

| Sterilization procedures for injection equipment not sufficient | ➔ Equipment potentially contaminated when re-used in IV injections |
| Use of multi-dose drug containers | ➔ Potential for contamination of the drug supply |
| Courses of multiple injections over 9-12 weeks | ➔ New HCV infected patients still returning for PAT while viremic |
| Injections given in mass setting to patients of all ages | ➔ Mixture of age cohorts with low and high prevalence of HCV (≠ childhood vaccination campaigns) |
| Patients sick with schistosomiasis, treatment had known side effects, cases of “post-injection hepatitis” considered common | ➔ Cases of symptomatic acute HCV infection may have been masked, outbreaks missed (~80% of new HCV infections silent anyway) |

Frank et al, Lancet 2000
HCV Seroprevalence Data Structure

- 8499 analyzed
- Sample size
- Community Study
- Work Migrant Study
- ≈ 50% male

Frank et al, Lancet 2000
Geographic HCV Prevalence

**EGYPT**
- **Upper Egypt**: 19.4% (95% CI: 17.2-21.6)
- **Lower Egypt**: 28.4% (95% CI: 27.1-29.2)
- **Middle Egypt**: 26.5% (95% CI: 23.7-29.4)
- **Alexandria**: 5.9% (95% CI: 4.2-7.7)
- **Cairo**: 8.2% (95% CI: 6.7-9.8)

**Mediterranean Sea**
- **Libya**
- **Israel**
- **Red Sea**

*age-adjusted prevalence, sample aged between 10 and 50 years*

Frank et al, Lancet 2000
HCV Prevalence by Age and Region

Frank et al, Lancet 2000
Comparison of Exposure Index and Prevalence

Lower Egypt

Alexandria

Middle Egypt

Upper Egypt

Frank et al, Lancet 2000
HBV and HCV

Frank et al, Lancet 2000
Discussion

Can PAT explain Egypt’s high rate of HCV?

- History of PAT is recognized risk factor for HCV in Egypt
- HCV rates very high in age cohorts most affected by PAT
- PAT mass treatment had an especially high potential of transmitting HCV
- An HCV “epidemic” spread through PAT treatment centers is consistent with strong genotype homogeneity
- Current increase in cases of liver cancer corresponds to a cohort of new HCV infections 20-30 years ago
- Patterns of PAT use are still reflected in HCV prevalence rates by age and region
- HBV seroprevalence evidence is supportive of hypothesis

Frank et al, Lancet 2000
Why not other countries with Schistosomiasis?

• No other country with schistosomiasis used PAT as much as Egypt, because

  » schistosomiasis not as geographically widespread, prevalence not as high
  » schistosomiasis treatment not a political priority
  » no/less resources available
  » other approaches than intensive drug therapy worked (in some countries mollusciciding worked well)
  » health systems not as developed as Egypt’s

Frank et al, Lancet 2000
Conclusion

- HCV transmission through PAT is very likely explanation for Egypt’s high prevalence of HCV in most affected age cohorts
  - Born ~1950 to 1970 in Middle and Upper Egypt
  - Born ~ 1950 to 1980 in Lower Egypt

- Likely PAT played a strong role in spread of HCV in rural areas of Egypt

- After cessation of PAT (mid-1980s), a large reservoir of chronic infections provided for continued transmission through other routes of exposure

Frank et al, Lancet 2000
Conclusion

– Not a exercise in historical epidemiology, but identification of cohort of chronically infected

– Important, because
  - cohort now is now 20-30 years infected, develops complications
  - reservoir of chronic infections playing role in current transmission
Age distributions by group

Cases Group Mean Age = 23.9 +/-9.7 years (Median = 21)
Comparison Group Mean Age = 19.4 +/-2.3 years (Median = 19)

Favorov, CDC central Asia Progr.
Age distributions by group

Cases Group Mean Age = 23.9 +/- 9.7 years (Median = 21)
Comparison Group Mean Age = 19.4 +/- 2.3 years (Median = 19)

Cases – patients with jaundice and ALT elevation (> 5 times higher than normal) hospitalized at Infectious Disease Hospital Number 1 in Moscow, February–May, 1998. N = 430.

Favorov, CDC central Asia Progr.
Age distributions by group

Cases Group Mean Age = 23.9 +/-9.7 years (Median = 21)

Comparison Group Mean Age = 19.4 +/-2.3 years (Median = 19)

Reference group (Non-Sick) -- Volunteers from Medical High School and Pre-recruitment medical examination participants, with no history of jaundice. Collected April–June 1998. N=311

Favorov, CDC central Asia Progr.
Age distributions by group

Cases Group Mean Age = 23.9 +/-9.7 years (Median = 21)
Comparison Group Mean Age = 19.4 +/-2.3 years (Median = 19)

Favorov, CDC central Asia Progr.
Parenteral Exposure among HBV, HCV Patients and Comparison Group

Invasive manipulations during last 6 month

Favorov, CDC central Asia Progr.
Blood Transfusion among HBV, HCV Patients and Comparison Group

Favorov, CDC central Asia Progr.
At Least One Visit to the Dentists with Parenteral Exposure among HBV, HCV Patients and Comparison Group

Favorov, CDC central Asia Progr.
Illicit Drug Use among HBV, HCV Patients and Comparison Group

Transfusion, Hospitalization, Dentist & Ambulatory Treatment Excluded
Number of Sexual Partners (last 6 month) among HBV, HCV Patients and Comparison Group (other risk factors excluded)

Favorov, CDC central Asia Progr.
### Selected Risk Factors* Population Attributable Risk for HBV/HCV patients in Moscow Russia, 1998.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>HBV N=274</th>
<th>HCV N=62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Illicit Drug Abuse</td>
<td>79%</td>
<td>87%</td>
</tr>
<tr>
<td>Outpatient treatment</td>
<td>39%</td>
<td>34%</td>
</tr>
<tr>
<td>Dentists</td>
<td>14%</td>
<td>n.a.</td>
</tr>
<tr>
<td>Hospitalization</td>
<td>12%</td>
<td>8%</td>
</tr>
<tr>
<td>Tattoo</td>
<td>4%</td>
<td>n.a.</td>
</tr>
<tr>
<td>10 and more sexual partners (last 6 month)</td>
<td>3%</td>
<td>n.a.</td>
</tr>
<tr>
<td>History of Syphilis</td>
<td>12%</td>
<td>n.a.</td>
</tr>
</tbody>
</table>

** - Not applicable  

Favorov, CDC central Asia Progr.
Conclusions

- Injection drug use with unsafe injection practice strongly associated with acquiring acute hepatitis B and C in Moscow.
- Outpatients treatment remain highly associated with acquiring acute hepatitis; attributable risk for non-drug users HBV patients 39%, HCV 34%.
- Hospitalization, tattooing, multiple sexual contacts demonstrated attributable risk for non-drug users 3 – 12%

Favorov, CDC central Asia Progr.
Hepatitis C: WHO recommends (1)

1. International consensus for surveillance, diagnosis, control, treatment

2. Prevention through appropriate screening of blood products should be performed on a global scale

3. Universal precautions in health care settings:
   Disposable medical material is not reused
   Reusable material is appropriately sterilized
Hepatitis C: WHO recommends (2)

4. Public education about the risks of using unsterilized material should be promoted.

5. Investigation of transmission modes, in order to establish effective prevention methods. (vaccine not available)

6. Standardization of diagnostic reagents/procedures. True confirmatory tests should be developed. Quality control should be developed.
7. Diagnostic tools differentiating recovery, healthy carrier state and chronic aggressive disease should be developed

8. Improve global surveillance
   Figures are based on blood donors, not general population

9. Understand epidemiology, clinical and immune-pathological importance, susceptibility to treatment of different HCV genotypes or serotypes
Hepatitis C Conclusions

- A new disease (among others) places extensive pressure and additional financial burden upon communities.
- Natural history of hepatitis C indicates that benefits can only be expected in the long term.
- No vaccine, treatment is expensive and difficult.
- Insufficient epidemiological information in most countries.
- Prevention methods have not been validated in most instances.
Recommendations

- Promote the use of single use syringes and needles (auto-disable) in Moscow
- Promote infection control practices in drug use communities in Moscow
- Educate drug use communities members and health care workers about the risks associated with re-use injection material

Favorov, CDC central Asia Progr.
WHO’s mission

- Norms and standards
- Technical support
- Transfer of knowledge
- Advocacy tools to assist countries to access bilateral support
- Coordinate intercountry activities
- Assistance with development of operational research
- (direct support) e.g. vaccines