WHO Guideline on Estimation of Residual Risk of HIV, HBV or HCV Infections via Cellular Blood Components and Plasma

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GL project leader

GL draft version (May 2016)
WHO Achilles Project (WHA 63.12)

Recovered plasma from whole blood donations

- Disposed as biological waste in many low and middle income countries

- > 9.3 million liters / year

- Plasma derived medicinal products (PDMPs) are imported at high cost

- Could be used as source for manufacture of PDMPs
WHO Achilles Project

- Plasma quality acceptable for fractionation
  - Good Manufacturing Practice (GMP)
  - Strengthening of Regulatory Oversight
  - Residual virus input in pools versus virus inactivation capacity

- Virus content in plasma pools dependent on
  - Screening tests
  - Virus epidemiology of donor populations
  - Biological features of viruses
WHO Achilles Project

- Measures for improvement of plasma quality (e.g. GMP introduction, screening for infectious markers)
  - Affect all blood products
  - Impact virus safety of cellular blood components
WHO Achilles Project

“WHO Guideline on Residual Risk Estimation”

- Requested by blood transfusion services in LMIC
- Endorsed by WHO ECBS in Oct 2012

Goals

- Impact of screening algorithms on blood safety
- Cost benefit of different testing algorithms
- Risk estimations (also on less detailed data base)
- Comparability between different blood establishments
- Has to be kept relatively simple, but state of the art
Residual Risk of HIV, HBV, HCV

Sources for residual risk for viruses in blood

- Assay failures
  - Malfunction instrument, software
  - Design non-detection of viral variants

- Diagnostic window period
  ( = phase elapsing between the time point of infection and first detectability of the viral marker by the screening assay)
  - All screening technologies, each assay
  - Differential size
  - Different viraemic levels
Residual Risk of HIV, HBV, HCV

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Diagnostic Window of HIV Infection

Early phase

- RNA
- p24-Ag
- antiHIV
- NAT Screening

Chronic phase

- RNA
- antiHIV

Residual Risk
- Weeks
- Years
Diagnostic Window of HIV Infection

Early phase
- p24-Ag
- RNA
- Residual Risk
- Weeks

Chronic phase
- antiHIV
- Virus concentration
- antiHIV
- RNA
- Years
Diagnostic Window of HIV Infection

Early phase
- RNA
- p24-Ag
- antiHIV

Chronic phase
- antiHIV

Residual Risk
- Virus concentration

Weeks

Years
Who Guideline on Residual Risk Estimation

Definitions chosen in the RR GL

- Assay categories
  - NATs (ID, MP16)
  - Antigen assays (HIV, HBV, HCV)
  - Combo assays (HIV, HCV)
  - Antibody assays (HIV, HCV)
  - Rapid diagnostic tests (HIV, HBV, HCV)

Limitation:

Features of individual assays within category vary
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Definitions chosen in the RR GL

- Length of viraemic phase of diagnostic window for assay categories
  - Viraemic phase: \( \geq 1 \) virus particle / 20 ml plasma
  - Mean for respective assay category (CE, FDA, WHO PQ IVD, …)

→ Table 1 of the GL

Limitation

Worst case of potential infectivity of blood components
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Lengths of viraemic phase of **diagnostic windows** with reference to **screening test categories** (Table 1)

<table>
<thead>
<tr>
<th></th>
<th>Length of the viraemic phase of the diagnostic window period (vDWP) for test categories (in days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NAT ID</td>
</tr>
<tr>
<td>HIV</td>
<td>8</td>
</tr>
<tr>
<td>HBV</td>
<td>27</td>
</tr>
<tr>
<td>HCV</td>
<td>5</td>
</tr>
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</table>
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Lengths of viraemic phase of diagnostic windows with reference to screening test categories (Table 1)

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<tr>
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<th>HBV</th>
<th>HCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lengths</td>
<td>8</td>
<td>27</td>
<td>5</td>
</tr>
<tr>
<td>Diagnostic windows</td>
<td>11</td>
<td>37</td>
<td>7</td>
</tr>
<tr>
<td>Viraemic phase</td>
<td>14</td>
<td>42</td>
<td>9</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>16</td>
<td>---</td>
<td>38</td>
</tr>
<tr>
<td>Corresponding window period of the assay</td>
<td>21</td>
<td>55</td>
<td>60</td>
</tr>
<tr>
<td>Risk calculation</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
</tbody>
</table>

These estimates should be used for risk calculation unless there is more detailed information available for the sensitivity and corresponding window period of the assay.
Residual Risk per Blood Donation

- Frequency of window phase donations depends on the virus epidemiology of the donor population.

- Donor populations
  - First time donors
  - Repeat donors

- Positive test results in repeat donors provide information on incidence = rate of new infections in a certain time period.
Repeat Donors
Repeat Donors

infection
Repeat Donors

infection
Repeat Donors

window phase donation

infection
Incidence (Repeat Donors)

Repeat Donors (RD)

- Probability of viraemic window phase donations dependent from
  - Infection rates in the population (incidence)

\[
\text{Incidence} = \frac{\text{number of repeat donors tested positive during one year}}{\text{total number of repeat donors in the year}} \times 100000
\]
Calculation of Residual Risk (Repeat Donors)

Residual Risk (RR) per donation

- Number of seroconversions (one year observation period)
- Donation frequency: interdonation intervals (IDI)
- Screening test category: length of viraemic diagnostic window phase (vDWP)

\[
RR = \frac{vDWP}{IDI} \times \frac{\text{number of seroconverters among repeat donors}}{\text{number of donations from repeat donors}}
\]
Early infection phase

- 70% transient
- 25% transient (no detectable HBsAg)
- 5% chronic

HBV incidence adjustment factor
- underestimation by transient direct screening marker(s)
- assay sensitivity / interdonation interval
Interdonation Interval (IDI) Adjustment

- Length of IDI determines probability for window phase donations

- Adjustment for IDIs significantly different between seroconverting and non-seroconverting donors
Residual Risk Estimation (First Time Donors)

First Time Donors (FTD)

- Positive test result may reflect past (prevalent) or recent (incident) infection
- Investigations (NAT, detuned antibody assays) needed to estimate recent infections (incidence) in FTD
- Investigations of different donor populations show 2 – 3 fold incidence in FTD compared to RD

**FTD incidence adjustment factor of 3** (worst case)
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- Calculation of frequency of viraemic donations
- Comparisons between donor populations
- Impact of testing algorithms on transfusion and plasma safety
  - Cost benefit analysis for different testing algorithms

**Limitation:** worst case: “each viraemic donation infectious”
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- Maximal virus concentration during diagnostic window
  - For risk modelling of plasma pool contamination
  - Dependent on assay categories

- Contamination frequency and contamination level of manufacturing plasma pools
  - Inventory hold
  - Virus inactivation capacity

**worst case**

“each viraemic donation with maximal virus concentration”
### WHO Guideline on Residual Risk Estimation

Maximal virus concentration in window phase donations

<table>
<thead>
<tr>
<th></th>
<th>NAT ID</th>
<th>NAT MP (16)</th>
<th>antigen ELISA / CLIA</th>
<th>combo ELISA / CLIA</th>
<th>antibody ELISA / CLIA</th>
<th>antigen RDT</th>
<th>combo RDT</th>
<th>antibody RDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>150</td>
<td>2400</td>
<td>$2 \times 10^4$</td>
<td>$10^5$</td>
<td>$10^7$</td>
<td>---</td>
<td>$10^7$</td>
<td>$10^7$</td>
</tr>
<tr>
<td>HBV</td>
<td>24</td>
<td>384</td>
<td>$10^3$</td>
<td>---</td>
<td>$3 \times 10^4$</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>HCV</td>
<td>30</td>
<td>480</td>
<td>$10^4$</td>
<td>$5 \times 10^6$</td>
<td>$10^8$</td>
<td>---</td>
<td>---</td>
<td>$10^8$</td>
</tr>
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</table>
WHO Guideline on Residual Risk Estimation

- Annexes
  - Recommendations for targeted performance evaluation of screening tests
  - Examples for RR calculations
WHO Guideline on Residual Risk Estimation

Current status (05/2016)

- Draft guideline prepared by group of experts
- Presented to ECBS and BRN 2015
- Guideline consultation phases, comments still welcome
- Will be proposed for adoption by ECBS 2016
WHO Guideline on Residual Risk Estimation

Conclusions

- Differential benefit of screening options
  - Virus transmissions by blood components
  - Plasma pool contamination
- Consistency of calculations between establishments
- Decisions on testing strategies
- Consistent with EMA PMF approach to estimate plasma pool contamination
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Thanks to …

RR Working Group

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Blood Regulator Network Members
WHO Guideline on Residual Risk Estimation

THANK YOU