New Trends in Infection Protection of Transfusion Recipients

Christoph Niederhauser
Topics

• History and current situation
• Possible intervention tools
• (Re)emerging infectious disease agents (EIDs)
• Positive cases versus costs
• New approaches / glance into the crystal ball
Evolution of the test menu

What's on the doorstep:

- HEV
- CMV
- WNV
- Chikungunya Virus
- Zika Virus
- Dengue Virus
- Coxiella burnetti
- ........

Parvovirus B19 NAT
HAV NAT  HEV NAT
HBV NAT

Anti-T. cruzi
HIV NAT

HCV & HIV NAT
HCV Ag

Anti-HCV

& further marker, country- or region specific:

Malaria (2007)
Leishmania
Dengue
Chagas (2013)
Babesia
Etc……

Syphilis 1938
HBsAg

ALAT

Anti-CT

Anti-CMV

Anti-HBc

ALAT

Anti-HTLV

HCV Ag

1938
1970
1975
1980
1985
1990
1995
2000
2005
2010
2015
2020

Swisstransfusion Bern | CNI | August 2018 | page 3
Theoretical calculated residual risks

Risk of a NON-Detection of HBV, HIV and HCV

<table>
<thead>
<tr>
<th>Virus</th>
<th>Last TTID</th>
<th>Theoretical not detected contaminated blood donation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>2009</td>
<td>Every 3 years</td>
</tr>
<tr>
<td>HIV</td>
<td>2002</td>
<td>Every 22 years</td>
</tr>
<tr>
<td>HCV</td>
<td>Before 1999</td>
<td>Every 39 years</td>
</tr>
</tbody>
</table>

2015-2017:
- HIV 1 : 8.9 Millionen
- HCV 1 : 13 Millionen
- HBV 1 : 240’000 / 880’000
5 layers for safe blood components
Current potential intervention tools

- Possible interventions dependent on the epidemiological situation
  - Permanent exclusion
  - Deferral of the donors for a defined time
  - General screening of all donations
  - Targeted testing (donors at-risk, defined groups of patients, etc.)
  - Seasonal screening for specific microbial threats
  - Indirect detection (Ab) (chronic infections)
  - Direct detection (Antigen or NAT) (acute infections)
Potential intervention tools (cont.)

- Pre-donation bag
- Leucocyte depletion
- Pathogen reduction technologies
- After donation information (NSI)
- Risk assessment
- Preparedness plans
- Monitoring / Surveillance
- **Future**: what does the crystal ball tell us?
Definition of (Re)emerging infectious disease agent (EID)

- Increasing incidence in humans during the last two decades either:
  - as a new infection
  - as a known infection introduced in new populations
  - (or increased awareness of an existing infection)

- EIDs are relevant to blood safety if the pathogen:
  - has an asymptomatic phase
  - is present in the blood
  - can survive blood processing and storage
  - can establish a clinically relevant infection in the recipient

(Re)emerging infectious disease agents

- The fact that (re)emerging disease bugs are entering industrialised countries, such as Europe or the USA is a consequence of the high mobility of people, animals, goods, vectors, microbes and the recent climatic changes.

- Establishment of a mosquito population.
New Kids
(Actors and their supporting players)

Plasmodien ssp. (Malaria)
Trypanosoma cruzi (Chagas)
West Nile Virus
Chickungunya Virus
Zika Virus
Hepatitis E Virus
Dengue Virus
Usutu Virus
Borna Virus

........
But despite the probable low risk there is still likely to be a considerable amount of effort and investment in infectious disease testing in the near future and especially in the field of EIDs.

- Decision making should contain the following steps:
  - Risk assessment (epidemiological data, risk calculations, cost-benefit, etc.)
  - Risk management (definition of possible approaches, monitoring, etc.)
  - Risk communication (authorities, donors, patients, employees, general population, etc.)
Infectious disease agents with potential for TTIDs:

<table>
<thead>
<tr>
<th>Viruses</th>
<th>Bacteria</th>
<th>Parasites</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Treponema</td>
<td><em>Plasmodium ssp.</em> (Malaria)</td>
</tr>
<tr>
<td>Hepatitis Viruses (HAV, HBV, HCV, HEV)</td>
<td>Coxiella</td>
<td><em>Trypanosoma cruzi</em> (Chagas)</td>
</tr>
<tr>
<td>CMV</td>
<td>Yersinia</td>
<td>Babesia</td>
</tr>
<tr>
<td>HTLV 1/2</td>
<td>Salmonallla</td>
<td>Toxoplasma</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Shigella</td>
<td>………….</td>
</tr>
<tr>
<td>West Nile Virus</td>
<td>Borrelia</td>
<td></td>
</tr>
<tr>
<td>Chikungunya Virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dengue Virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zika Virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronavirus (SARS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GBV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>XMRV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usutu Virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ross River Valley Virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Japanese Enzephalitis Virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Borna Virus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission of neurodegenerative disorders</td>
<td></td>
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<tr>
<td>………….</td>
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<td></td>
</tr>
</tbody>
</table>

• Currently approximately 70 microbes (viruses, parasites and bacteria) which could lead to blood borne infections (Stramer et al. Vox Sang, 2009)
Example of a selective testing approach in Switzerland

Implemented since 2007 (Malaria) and since 2013 (Chagas) as selective questionnaire based assays

Successful: more than 240 (Malaria) and 6 (Chagas) cases detected

No transfusion transmitted case since 1999 (Malaria) and 2008 (Chagas)

Not labour intensive

Minimal cost if compared to other infectious disease agents

Very cost efficient
West Nile Virus

• Huge epidemic in the US since 2000 as a trigger for European Countries

• Some smaller local outbreaks in Europe

• **Preparedness** plan was worked out by a B-CH working group. Estimating risks, proposing measures and defining sensitivity limit, validation of the assay and preparing the Blood Bank IT systems

• Information and consequent questionnaire for a **temporary deferral or testing** of the donors

• Within 2 weeks Swiss **blood donor screening** should be in routine

• Switzerland is ready for the case of an epidemic
Epidemic in La Réunion March 2005 until February 2006; approximately 266,000 human beings infected (1/3 of the population of that island); 254 deaths

Blood products were imported from the mainland France

A in-house PCR was developed by the national reference laboratory in Bern

Today there are existing commercial available assays on the market

A transfusion-transmission of that virus has never been proved despite several huge outbreaks through over the world

That virus probably poses no risk for the recipients of blood products
Zika Virus

- Infection routes
  - Mosquitos (Aedes africanus, aegypti, albopictus)
  - Intrauterine (Rasmussen et al. 2016)
  - Sexual intercourse (D’Ortenzio et al. 2016)
  - Up to 2/3 of the population can be infected, Brazil assumed in 2015 between 500’000 up to 1’500’000 possible infections
  - Blood components (????): despite huge epidemics over the last years up to today no really proven TT-Zika infection

- Prepardness plan exists
  - Temporally deferral of donors
  - Assays in validation, IT blood bank system
Hepatitis E Virus

- Seroprevalence in Switzerland about 20%; Genotype 3 predominant in Europe
- Main route of infection is not or badly cooked pork meat
- Incidence in blood donors 1:700 up to 1:14’000 depending on assay, region, food production, population, etc.
- In most cases immunocompetent individuals with no symptoms and no complications
- Immunosuppressed patients / pre-damaged liver disease are at risk
- About 100 TT-HEV documented
- If blood component is HEV contaminated about 40% are transmitted
- HEV notification of HEV RNA positive individuals mandatory since January 2018 (FOPH)
- NAT Screening in Switzerland will be mandatory since October 2018 (sensitivity limit of 450 IU/ml individual donation)
Deferrals of blood donors with a history of CFS or prostate cancer have been implemented in several countries as a precautionary measure until more data have been published (US, Canada, Australia).

Results suggest that the association of XMRV with human disease is due to contamination of human samples with virus originating from this recombination event.
### Detected confirmed positive TTID

<table>
<thead>
<tr>
<th></th>
<th>2007 - 2017 ~4.2 millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>17 FD / 22 RD</td>
</tr>
<tr>
<td>HCV</td>
<td>167 FD / 18 RD</td>
</tr>
<tr>
<td>HBV</td>
<td>331 FD / 71 RD</td>
</tr>
<tr>
<td>Syphilis</td>
<td>175 FD / 71 RD</td>
</tr>
<tr>
<td>Malaria</td>
<td>248 (4.5 Mio / 16’218)+</td>
</tr>
<tr>
<td>Chagas</td>
<td>6 (1.5 Mio / 9590)°</td>
</tr>
<tr>
<td>HAV</td>
<td>0 (0.8 Mio)*</td>
</tr>
<tr>
<td>Parovirus B19</td>
<td>31 (0.8 Mio)*</td>
</tr>
</tbody>
</table>

+ Since 2007
° Since 2013
* Since 2015
## Costs in terms of testing

<table>
<thead>
<tr>
<th>Type of testing</th>
<th>Period</th>
<th>Number of donations tested</th>
<th>Confirmed positive cases</th>
<th>Total costs (CHF)</th>
<th>Costs per case (CHF)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-HIV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>General Screening</td>
<td>1996 - 2016</td>
<td>8.4 Million</td>
<td>97</td>
<td>50.4 Million</td>
</tr>
<tr>
<td><strong>HIV-PCR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>General Screening</td>
<td>2003 - 2016</td>
<td>5.0 Million</td>
<td>1</td>
<td>40.0 Million</td>
</tr>
<tr>
<td><strong>Anti-HCV</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>General Screening</td>
<td>1996 - 2016</td>
<td>8.4 Million</td>
<td>616</td>
<td>50.4 Million</td>
</tr>
<tr>
<td><strong>HCV-PCR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>General Screening</td>
<td>2000 - 2016</td>
<td>6.5 Million</td>
<td>2</td>
<td>52.0 Million</td>
</tr>
<tr>
<td><strong>HBsAg</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>General Screening</td>
<td>1996 - 2016</td>
<td>8.4 Million</td>
<td>893</td>
<td>50.4 Million</td>
</tr>
<tr>
<td><strong>HBV-PCR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>General Screening</td>
<td>2008 - 2016</td>
<td>3.1 Million</td>
<td>48</td>
<td>24.8 Million</td>
</tr>
<tr>
<td><strong>Anti-T. pallidum</strong></td>
<td>General Screening</td>
<td>1996 - 2016</td>
<td>8.4 Million</td>
<td>542</td>
<td>50.4 Million</td>
</tr>
<tr>
<td><strong>HAV-PCR</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Parvovirus B19-PCR</strong></td>
<td>General Screening</td>
<td>2007 - 2016</td>
<td>3.5 Million</td>
<td>0</td>
<td>14 Million</td>
</tr>
<tr>
<td><strong>Anti-Plasmodium spp.</strong></td>
<td>Risk based testing</td>
<td>2007 - 2016</td>
<td>14'531</td>
<td>211</td>
<td>365'000</td>
</tr>
<tr>
<td><strong>Anti-T. cruzi</strong></td>
<td>Risk based testing</td>
<td>2013 - 2016</td>
<td>8'312</td>
<td>5</td>
<td>200'000</td>
</tr>
<tr>
<td><strong>West Nile-Virus</strong></td>
<td>General Screening</td>
<td>Preparedness-Plan</td>
<td>~150'000 (per season)</td>
<td>na</td>
<td>3 Million.</td>
</tr>
<tr>
<td><strong>Zika-Virus</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chikungunya-Virus</strong></td>
<td>General Screening</td>
<td>na</td>
<td>~150'000 (per season)</td>
<td>na</td>
<td>3 Million per year</td>
</tr>
<tr>
<td><strong>Hepatitis E-Virus</strong></td>
<td>General Screening</td>
<td>Coming soon</td>
<td>300’000 (per year)</td>
<td>100 (assumption)</td>
<td>1 Million per year</td>
</tr>
</tbody>
</table>
Concern about contaminated blood products is still present.
New infectious disease agents will be in the focus.

**Viruses**
- HIV
- Hepatitis Viruses (HAV, HBV, HCV, HEV)
- CMV
- HTLV 1/2
- Parvovirus B19
- West Nile Virus
- Chikungunya Virus
- Dengue Virus
- Zika Virus
- Coronavirus (SARS)
- GBV
- TTV
- XMRV
- Usutu Virus
- Ross River Valley Virus
- Japanese Enzephalitis Virus
- Borna Virus
- Transmission of neurodegenerative disorders

**Bacteria**
- Treponema
- Coxiella
- Yersinia
- Salmonella
- Shigella
- Borrelia

**Parasites**
- *Plasmodium* ssp. (Malaria)
- *Trypanosoma cruzi* (Chagas)
- Babesia
- Toxoplasma

**Prions**
- CJV
- vCJD

**Protheopathies**
What will bring the future?
Probable scenarios

- Climate changes, milder winter
- More mosquitos in Europe / Spread of ticks
- Increased travel / increased transport
- Increased migration / transportation

More (re)emerging infectious disease agents such as WNV, Dengue Virus, Usutu ?, new ones

- Pathogen reduction technology on a new level
  - Whole blood pathogen reduction in routine
  - The process is automated
  - The cost are low

one additional safety layer for all labile blood components (RBCs, Thrombocytes, Plasma)
Pathogen reduction technologies: the holy grail

• Pathogen reduction (PR) technologies as solution for all problems?
• Probably not:
  – Currently in Switzerland only one notified product available (monopoly position, withdrawal)
  – Only for Platelets and Plasma, not yet for whole blood
  – Not yet fully automated (very labour-intensive, many personal resources)
  – Not suitable for some infectious disease agents HEV, HAV (non-enveloped viruses) etc. HIV depending on the system
  – Different infectious diseases agents are reduced at different levels
  – “Very” expensive
  – Probably useful for new unknown infectious disease agents, question are these susceptible against the used PR system?
  – No “100 % safety”
Newest EIDs

- **Japanese Encephalitis Virus** transmitted via Blood Transfusion Hong Kong China (Cheng et al., Emerg Infect Dis 2018)

- **Australia Ross River Valley Virus**, the risk of RRV transfusion transmission in Australia is acceptably low and appropriately managed through existing risk management, including donation restrictions and recall policies (Faddy et al., Transfusion 2018)

- **Borna Virus**, two cases of transmission via organs in Germany (RKI Bulletin, 2018)

- **Babesia**, more than 165 documented transfusion-transmitted infections not yet a problem in Europe (Fang and McCullough, Trans Med Review 2016)

- **Dengue Virus, Usutu Virus** and other **Arboviruses** under surveillance

- Transmission of **neurodegenerative disorders**: Data provide no evidence for the transmission of neurodegenerative diseases (Edgren et al., Ann Int Med 2016)
Testing strategies: How to continue

- Abolishment of serological testing, first HBsAg, then Syphilis, ……………
- Less sensitive NAT assays (Minipooling)
- NAT Multiplexing of different viruses such as HIV, HCV and HBV
  - Example: Dengue, ZIKAV, CHIKV, USUTUV, WNV, etc.
- Point of care testing (new NAT systems such as LIAT etc.) CMV
- Residual risk calculations; cost benefit calculations, comparison to other routes of infection (food, airborne, water, etc. risk weighing)
- Automated pathogen reduction systems for whole blood
- Most important is the surveillance of new (re)emerging infections disease agents, in collaboration with other countries
- National and international working parties
Take home message

- Today our blood products are very safe
- Costs compared to the medical benefit are higher than in other medical disciplines
- Different measures can be taken to obtain safe blood components
- New infectious disease agents must be observed and if possible epidemiological data must be collected for Switzerland and the Swiss donor population
- Risk assessments must be performed
- New technologies must be observed, qualified and tested
- New approaches need to be considered
- Monitoring and surveillance are very important
- Currently there are no clearly defined goals or measures for the near future
Thank you very much for your attention

Special thanks to:
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