Donor health studies

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Zika risk assessment: Incidence of transfusion during pregnancy

Zika infection in 1\textsuperscript{st} and 2\textsuperscript{nd} trimester associated with microcephaly
Zika infection in 3\textsuperscript{rd} trimester associated with late-onset microcephaly?

In non-endemic areas:
What is the risk of donation from an infectious donor?
What is the risk of transfusing that unit to a pregnant woman?
Transfusion of pregnant women in Denmark and Sweden

Denmark – pregnancies and transfusions 2000-2008

<table>
<thead>
<tr>
<th>Year</th>
<th>Births</th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
<th>Total transfusions in Denmark</th>
<th>% units transfused to pregnant women</th>
<th>% units transfused to women in 1st and 2nd trimester</th>
<th>Units per 1,000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>66,651</td>
<td>33</td>
<td>47</td>
<td>143</td>
<td>426,208</td>
<td>0.052</td>
<td>0.019</td>
<td>3.3</td>
</tr>
<tr>
<td>2001</td>
<td>64,698</td>
<td>33</td>
<td>49</td>
<td>116</td>
<td>458,452</td>
<td>0.043</td>
<td>0.018</td>
<td>3.1</td>
</tr>
<tr>
<td>2002</td>
<td>63,382</td>
<td>54</td>
<td>37</td>
<td>222</td>
<td>501,407</td>
<td>0.062</td>
<td>0.018</td>
<td>4.9</td>
</tr>
<tr>
<td>2003</td>
<td>63,868</td>
<td>23</td>
<td>49</td>
<td>220</td>
<td>490,803</td>
<td>0.059</td>
<td>0.015</td>
<td>4.6</td>
</tr>
<tr>
<td>2004</td>
<td>63,918</td>
<td>30</td>
<td>29</td>
<td>156</td>
<td>449,405</td>
<td>0.048</td>
<td>0.013</td>
<td>3.4</td>
</tr>
<tr>
<td>2005</td>
<td>63,512</td>
<td>45</td>
<td>38</td>
<td>169</td>
<td>444,289</td>
<td>0.057</td>
<td>0.019</td>
<td>4.0</td>
</tr>
<tr>
<td>2006</td>
<td>64,226</td>
<td>33</td>
<td>52</td>
<td>159</td>
<td>451,685</td>
<td>0.054</td>
<td>0.019</td>
<td>3.8</td>
</tr>
<tr>
<td>2007</td>
<td>63,928</td>
<td>24</td>
<td>50</td>
<td>198</td>
<td>450,716</td>
<td>0.060</td>
<td>0.016</td>
<td>4.3</td>
</tr>
<tr>
<td>2008</td>
<td>64,211</td>
<td>17</td>
<td>35</td>
<td>149</td>
<td>442,264</td>
<td>0.045</td>
<td>0.012</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Sum/mean | 578,394 | 292 | 386 | 1,532 | 4,115,229 | 0.054 | 0.016 | 3.8 |
Transfusion of pregnant women in Denmark and Sweden

Sweden – pregnancies and transfusions 2000-2010

<table>
<thead>
<tr>
<th>Year</th>
<th>Births</th>
<th>1st trimester</th>
<th>2nd trimester</th>
<th>3rd trimester</th>
<th>Total transfusions in Sweden</th>
<th>% units transfused to pregnant women</th>
<th>% units transfused to women in 1st and 2nd trimester</th>
<th>Units per 1,000 births</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>87,250</td>
<td>48</td>
<td>68</td>
<td>437</td>
<td>624,154</td>
<td>0.089</td>
<td>0.019</td>
<td>6.3</td>
</tr>
<tr>
<td>2001</td>
<td>87,926</td>
<td>34</td>
<td>45</td>
<td>380</td>
<td>592,107</td>
<td>0.078</td>
<td>0.013</td>
<td>5.2</td>
</tr>
<tr>
<td>2002</td>
<td>92,152</td>
<td>46</td>
<td>79</td>
<td>283</td>
<td>576,704</td>
<td>0.071</td>
<td>0.022</td>
<td>4.4</td>
</tr>
<tr>
<td>2003</td>
<td>94,604</td>
<td>71</td>
<td>43</td>
<td>394</td>
<td>672,820</td>
<td>0.076</td>
<td>0.017</td>
<td>5.4</td>
</tr>
<tr>
<td>2004</td>
<td>95,101</td>
<td>170</td>
<td>96</td>
<td>367</td>
<td>672,614</td>
<td>0.094</td>
<td>0.040</td>
<td>6.7</td>
</tr>
<tr>
<td>2005</td>
<td>94,627</td>
<td>97</td>
<td>62</td>
<td>570</td>
<td>678,802</td>
<td>0.107</td>
<td>0.023</td>
<td>7.7</td>
</tr>
<tr>
<td>2006</td>
<td>97,226</td>
<td>123</td>
<td>154</td>
<td>637</td>
<td>691,146</td>
<td>0.132</td>
<td>0.040</td>
<td>9.4</td>
</tr>
<tr>
<td>2007</td>
<td>97,536</td>
<td>73</td>
<td>90</td>
<td>325</td>
<td>714,968</td>
<td>0.068</td>
<td>0.023</td>
<td>5.0</td>
</tr>
<tr>
<td>2008</td>
<td>98,659</td>
<td>57</td>
<td>80</td>
<td>424</td>
<td>723,143</td>
<td>0.078</td>
<td>0.019</td>
<td>5.7</td>
</tr>
<tr>
<td>2009</td>
<td>99,372</td>
<td>73</td>
<td>108</td>
<td>590</td>
<td>743,006</td>
<td>0.104</td>
<td>0.024</td>
<td>7.8</td>
</tr>
<tr>
<td>2010</td>
<td>103,814</td>
<td>55</td>
<td>234</td>
<td>658</td>
<td>720,608</td>
<td>0.131</td>
<td>0.040</td>
<td>9.1</td>
</tr>
<tr>
<td>Sum/mean</td>
<td>1,048,267</td>
<td>847</td>
<td>1,059</td>
<td>5,065</td>
<td>7,410,072</td>
<td>0.094</td>
<td>0.026</td>
<td>6.7</td>
</tr>
</tbody>
</table>
Transfusion of pregnant women in Denmark and Sweden

- 11,525,301 units and 1,626,661 pregnancies
- Percentage of products used for pregnant women was low but much higher in Sweden than in DK (0.094% vs. 0.054%)
- The number of units used per pregnancy is about 75% higher in Sweden (6.7 vs. 3.8 units/1,000 pregnancies)
- 1-2 women per 1,000 pregnancies require transfusion

Conclusion
- 5-9 per 10,000 units of blood are transfused to pregnant women
Low hemoglobin and risk of infection

- Low Hb is associated with poor general health and linked to anemia of chronic disease => increased risk of infection?
- Iron is needed by replicating microorganisms => decreased risk of infection?
- Association between Hb and risk of infection among healthy individuals not yet investigated.
- 1998-2012: 497,390 donors; 5,458,499 donations; window: 3 months after each donation; 1,339,362 person years of observation
## Low hemoglobin and prescriptions of anti-microbials

<table>
<thead>
<tr>
<th></th>
<th>Pre-menopausal women</th>
<th></th>
<th>Post-menopausal women</th>
<th></th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Person years at risk</td>
<td>HR</td>
<td>95%CI</td>
<td>Events</td>
</tr>
<tr>
<td>Deferral 12.6/13.6 g/dL</td>
<td>29,539</td>
<td>74,158</td>
<td>0.92</td>
<td>0.91-0.93</td>
<td>3,741</td>
</tr>
<tr>
<td>No deferral (reference)</td>
<td>159,025</td>
<td>375,022</td>
<td>1</td>
<td></td>
<td>41,685</td>
</tr>
<tr>
<td>Very low Hb &lt;0.1%</td>
<td>167</td>
<td>517</td>
<td>0.8</td>
<td>0.67-0.93</td>
<td>46</td>
</tr>
<tr>
<td>No very low Hb (reference)</td>
<td>188,397</td>
<td>448,663</td>
<td>1</td>
<td></td>
<td>45,380</td>
</tr>
</tbody>
</table>

Adjusted for age, similar when stratified for previous year donation frequency.
Low hemoglobin and risk of infection

Conclusions:

• Hb below deferral guidelines was not associated with risk of hospital contact due to infection.

• Hb below deferral guidelines was associated with a slightly reduced risk of filling a prescription for antimicrobials:
  \[ \text{HR: } 0.91 - 0.93 \]
  (Kotze et al, in revision)

Upcoming: Nation-wide pseudo-cluster-randomised trial of ferritin-guided iron supplementation:
Does iron supplementation affect risk of infection?
The Danish Blood Donor Study - Status

Initiated March 2010
110,000 blood donors have been included
Work dataset: 92,000 participants; 350,000 person-years of follow-up by June 2015
All baseline samples transferred to automated sample management system
DNA purified from 55,000 samples
>600,000 plasma archive samples from every donation available for research
S. aureus colonisation among healthy individuals

• A nasal swab has been obtained from 2,500 donors; aim 10,000

• Primary aim: to study the associations of S. aureus colonisation with morbidity (infections, metabolic disorders, autoimmune diseases)

• Secondary aims: Nasal microbiome and donor morbidity S. aureus/nasal microbiome and recipient outcome
### Nasal *S. aureus* colonisation among healthy individuals

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td><em>S. aureus</em> positive</td>
<td></td>
<td><em>S. aureus</em> negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>n</strong></td>
<td>758</td>
<td>246 (32)</td>
<td>512</td>
<td>68 (68)</td>
</tr>
<tr>
<td><strong>%</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of participants:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age&lt;25:</td>
<td>144</td>
<td>58 (40)</td>
<td>86</td>
<td>60 (60)</td>
</tr>
<tr>
<td>25≤age&lt;35:</td>
<td>198</td>
<td>74 (37)</td>
<td>124</td>
<td>63 (63)</td>
</tr>
<tr>
<td>35≤age&lt;45:</td>
<td>129</td>
<td>41 (32)</td>
<td>88</td>
<td>68 (68)</td>
</tr>
<tr>
<td>45≤age&lt;55:</td>
<td>155</td>
<td>39 (25)</td>
<td>116</td>
<td>75 (75)</td>
</tr>
<tr>
<td>Age≥55:</td>
<td>132</td>
<td>34 (26)</td>
<td>98</td>
<td>74 (74)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>26.8</td>
<td>(26.1-28.6)</td>
<td>24.4</td>
<td>(23.9-24.9)</td>
</tr>
<tr>
<td></td>
<td>24.4</td>
<td>(23.9-24.9)</td>
<td>24.7</td>
<td>(24.4-25.1)</td>
</tr>
<tr>
<td></td>
<td>25.7</td>
<td>(25.4-26.1)</td>
<td>25.6</td>
<td>(25.3-25.9)</td>
</tr>
<tr>
<td><strong>Current smoker (%)</strong></td>
<td>10.2</td>
<td>6.4</td>
<td>12.1</td>
<td>9.2</td>
</tr>
</tbody>
</table>

*S. aureus* colonisation: lower with age (OR=0.85 with 10 year older), smoking (OR=0.51) and female sex (OR=0.60)

Enhancement broth: more *S. aureus* than previously thought

Women have lower concentrations of bacteria than men

Decreasing smoking prevalence: the reason for the increasing prevalence of *S. aureus* colonisation?

Colonisation and transfusion risk?
S. aureus colonisation and HLA

HLA-DR15 is associated with colonisation
Odds ratio for DR15 carrier: 1.84 (CI: 1.08-3.16)

Tendency for HLA-DQ6:
Odds ratio 1.55 (CI: 0.98-2.45)

Kotb et al, Nature Medicine 2012
Invasive group A streptococcal infections:
Patients with the DRB1*1501/DQB1*0602 haplotype mounted significantly reduced responses and were less likely to develop severe systemic disease (P < 0.0001).
Risk assessment of donors using hematology analyzer data (unfortunately not infection-related...)

Prediction of chronic lymphatic leukemia

• Sysmex and hemoglobin measurements:
  Full white cell differential: 65,000 measurements /y
  Red cell parameters: approx. 150,000 measurements /y

Proof of concept:

• One small donation facility: 118,430 lymphocyte measurements from 15,448 donors during 13 years
• 32 donors had 1 to several measurements of lymph. >5
• 7 donors subsequently diagnosed with CLL
• HR: 1499 (95% CI: 270-8317)
Criteria: age > 40 years and lymph. > 5 \times 10^9 \text{ cells/L} \\
Sensitivity: 100\% (59-100) \\
Specificity: 99,94\% (99,89-99,97) \\
Positive predictive value: 41\% (18-67)
Conclusions

- We bleed donors with CLL

No evidence of transmission of chronic lymphocytic leukemia through blood transfusion

Henrik Hjalgrim,¹ Klaus Rostgaard,¹ Senthil K. Vasan,² Henrik Ullum,³ Christian Erikstrup,⁴ Ole B. V. Pedersen,⁵ Kaspar R. Nielsen,⁶ Kjell-Einar Tjøttstad,⁷ Mads Melbye,¹ Olof Nyrén,² and Gustaf Edgren²,⁸

(Blood 2015)

- Donors should be informed and offered counselling
- New medicine – early intervention may be feasible for some mutations
- Sysmex data – immense possibilities
Upcoming:

Donor disclosure
• Collaboration with Brian Custer

GWAS
• 20,000 samples to be typed
• Collaboration with deCode
• Research and blood center operation:
  Blood types and HLA types to be imputed
Donor disclosure

• 5,458,499 donations, 414,119 prescriptions for antimicrobials filled within 3 months of donation

• Incidence rate of 0.3 prescriptions/year

• 7.6% of our donors fill a prescription for an antimicrobial within 3 months of each donation

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• How many fill a prescription within 2 weeks of donation?

• Could some of the infections affect recipient health?
The Danish Blood Donor Study

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• Sebastian Kotzé
• Mikkel Steen Petersen
• Bjame Møller
• Khoa Manh Dinh
• Christina Stilling

Dept. of Clinical Immunology, Naestved Hospital:
• Ole Birger Pedersen

Dept. of Clinical Immunology, Aalborg University Hospital:
• Kaspar René Nielsen

The Blood Donors in Denmark
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• Poul Erik Herner Petersen

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• Lise Wegner Thørner
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• Mie Topholm Bruun

Dept. of Clinical Microbiology, Aarhus University Hospital:
• Lise Tomvig Erikstrup
Give blood, save lives, create knowledge