Residual infectious risks in blood transfusion
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Summary
Although blood transfusion in developed countries is extremely safe, transmission of infections still occurs. Despite the tremendous improvement of blood safety over the last 30 years, a residual risk remains of infectious donations slipping through, because of imperfect donor selection and the diagnostic window period. This thesis describes the yield of several safety measures concerning the infectious risks of blood transfusion in the Netherlands.

Previous donations from seroconverting donors are at risk to be infectious because of the possibility that the infection was not detected during the very early phase of infection. To obtain more insight in window period donations, it is important to assess the chances of transmission during the window period. This can be done through lookback procedures among recipients of pre-seroconversion donations (chapter 2). Of the 50 repeat donors seroconverting for HBV (n = 32), HCV (n = 3), HIV (n = 14) and HBV + HIV (n = 1) who triggered lookback procedures of 96 pre-seroconversion donations 2/39 (5%) tested recipients were found to be HBV infected. These two recipients were associated with the same donation. The repository sample of this donation tested positive for HBV DNA. Another recipient who tested positive for HIV was most likely infected before transfusion. No transmission occurred by donations which tested negative by PCR in repository pre-seroconversion samples. The yield of this labour intensive lookback procedure, considering the limited number of tested recipients and the identified number of infections, is low. The low number of tested recipients can be explained by various reasons: the physician decided not to test; the recipient had died; and failure of traceability by imperfect registration.

To reduce the rate of transfusion transmitted hepatitis B virus, HBV DNA testing for routine in-process testing for plasma fractionation was introduced in July 2006 and for all blood donations in November 2008. The introduction of the HBV DNA screening of Dutch blood donors resulted in 23 HBV NAT only donations (HBsAg negative and HBV DNA positive). The categorization with serology and molecular analysis of HBsAg negative and HBV DNA positive “healthy” donors is described in chapter 3. The majority of the identified donors were found to be chronically occult HBV (OBI) infected with very low levels of HBV DNA. Due to the low viremic levels, for only 6 of the 15 OBI donors HBV DNA could be sequenced. Five donors belonged to HBV genotype D with multiple escape mutations in the HBsAg a-determinant and CTL epitopes, while in the occult genotype A case the surface gene showed no mutations. Based on a test pool size of 6 donations, chronic occult HBV infection was detected in 1 per 155,532 Dutch donations. In 47% of OBI donors anti-HBs was negative, which is associated with higher infectivity. Other identified stages of HBV infection were very early pre-seroconversion stage of infection in four donors (genotype A2), suppressed acute HBV infection after vaccination in three donors (genotype A2) and acute HBV genotype G infection with hampered HBsAg production in one donor.

All previous donations of OBI donors are considered at risk to be infectious. For the acutely infected donors only the previous donations in the window-period, meaning all donations in the last 6 months preceding the last seronegative donation as described in chapter 2, are at risk. In chapter 4 the lookback results of 22 Dutch blood donors (in-
volving 448 blood components) who showed an HBV DNA-only test result are described. Sixteen of them were OBI donors. Donor triggered lookback procedures of window period donations of the acutely infected did not reveal transmission. Donor triggered lookback of OBI donations resulted in an observed low transmission rate of 5% (4/80 tested recipients). Three HBV infected recipients were associated with the same donor. The likelihood of transmission of HBV through blood transfusion was supported by genetical matches of the HBV strains in the donor and the recipients. This case clearly demonstrated that blood components from OBI donors can be infectious intermittently. A fourth recipient cleared the infection and could only be interpreted as probably infected through transfusion. Transmission was observed via all short shelf life blood components: red blood cell concentrates, platelet concentrate and fresh frozen plasma. Transmissions were not found via donations from anti-HBs positive OBI donors.

Chapter 3 and 4 relate to the period before the introduction of anti-HBc screening in July 2011. HBsAg negative, but HBV infected healthy blood donors cause the ongoing transmission of HBV via blood transfusion, if donor HBV screening is limited to HBsAg testing. HBV infection in OBI donors can be missed in HBV DNA screening, because of the low level of viremia. Additional screening for anti-HBc removes OBI from the blood supply. Together with HBV DNA screening all stages and variants of HBV infection are covered. The added value of HBsAg screening in the current Dutch test algorithm seems to be superfluous, but this needs to be explored further.

Donor selection and screening are important tools to reduce the risk of transfusion-transmissible infections (TTIs). TTIs are more common among new donors than repeat donors, as a result of the accumulation of chronic, yet undiagnosed infections. Acute infections among candidate (new) donors may occur as a result of unreported, recent risk behaviour (deferrable or non-deferrable) and test-seeking behaviour. Pre-donation screening of candidate donors without actual donation could prevent undetected window period donations during the first visit. Chapter 5 describes the value of pre-donation screening by comparing the proportion of incident TTIs in candidate donors, in first-time donors, and in repeat donors during the period 2009 to 2013. The proportion of incident infections among candidate donors/first-time donations/repeat donations was for HBV, 3.40/0/0.36; for HCV, 0/0/0.02; and for HIV, 0/0.69/0.14 per 100,000, respectively. The incidence in candidate donors was almost ten times higher than in repeat donors. Of the six candidate donors who were recently HBV infected, donor counselling revealed an explanation for the recent infection in 5 donors. One first-time donor, testing HIV-negative at predonation screening, tested positive for anti-HIV (confirmed by immunoblot) and HIV RNA in the first donation 29 days later. At the time of pre-donation screening the donor may have been infected with HIV with viremia below the limit of detection.

The study results indicate that in the Dutch setting predonation screening improves blood safety by reducing the chance of window infections. Further exploration of the reduction of residual risk by predonation screening, and of other aspects such as cost-effectiveness, is suggested.
Emerging infectious disease outbreaks abroad pose a threat to the safety of blood donated by travelling blood donors. Many blood banks have implemented temporary geographical deferral for donors who travelled to countries where (re)emerging infectious agents are prevalent. In practice, geographical deferral has been cumulatively implemented in the Netherlands, eventually for almost all countries outside Europe. Deferring donors temporarily will decrease the risk of infected donations, but the yield of this exclusion is unclear. Chapter 6 describes the yield of donor deferral after travelling by estimating the number of infected donors returning from 6 affected areas, using incidence estimations of infectious diseases in the outbreak region and Dutch tourist travel data. The yield of temporary exclusion of blood donors travelling to the specific areas was very low: deferral of donors who travelled to Central Macedonia excludes at most one WNV-infected donor per 3 years and deferral for donors returning from Thailand excludes one chikungunya-infected donor per 15 years. For the other outbreaks (WNV in Emilia Romagna, hepatitis A in Latvia, sand-fly fever in Tuscany and Turkey) the deferral would exclude one infected donor per 80 to 200 years.

Increased travelling and expansion of affected areas increase donor deferral. Monitoring new outbreaks leads to variable donor deferral over time and interventions are frequently implemented after an outbreak has occurred. Deferring too many donors may jeopardize the blood supply. To analyse the consequences of temporary donor deferral the travel behaviour (destination, frequency and time of travel in 2010) among Dutch blood donors was studied by means of a questionnaire (Chapter 7). The consequences for donor availability of two deferral policies was calculated: deferral by specific country versus universal deferral of at least 4 weeks after each stay outside Europe. The deferral for entire countries and universal deferral would lead to 11.1% and 11.4% decrease in donor availability, respectively. Universal deferral resulted in a limited additional decrease of 0.3% (95% CI 0.13-0.44) in donor availability and should therefore be considered as a simpler and safer measure.

A web-based tool, the European Up-Front Risk Assessment Tool (EUFRAT), can be used to quantify the transfusion transmission infectious risk from donations of donors returning from affected areas where an emerging infectious disease is prevalent. Local surveillance data on notified cases, travel behaviour of the donor population, donation pattern and derived components and disease specific parameters are needed as input parameters to estimate the risk. In chapter 8 we aim to validate the estimates of the number of Dutch donors that became infected when travelling to Suriname or the Dutch Caribbean (Aruba, Curacao, St. Maarten, Bonaire, St. Eustatius, and Saba) in the years 2001 through 2011, as obtained by the EUFRAT model. These estimates were compared with the actual number of dengue infections among Dutch travellers in the general population as obtained from a laboratory-based study. The expected cumulative number of donors becoming infected during travels to Suriname and the Dutch Caribbean from 2001 to 2011 was estimated at 5 (95%CI, 2-11) and 86 (45-179) respectively. The infection risk inferred from the laboratory-based study was respectively 19 (9-61) and 28 (14-92). Given the
independence of the data sources, these estimates are remarkably close. Additionally, the EUFRAT model can be used to estimate the expected number of transfusion transmission cases caused by infected travelling donors. The model estimated that without donor deferral, 0.02 (0.001-0.06) and 0.40 (0.01-1.4) recipients would have been infected by these travelling donors.