Residual infectious risks in blood transfusion
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General discussion
The studies in this thesis analyse the yield of several preventive measures targeted at specific small risks of transfusion transmitted infections (TTIs). In general, the yield of these measures was small while intensive labour and costs were involved. The yield of lookback procedures of pre-seroconversion donations and donations from donors with an “HBV DNA-only” test result (chapters 2-4) was limited to the 5% of exposed recipients who were found to be infected. The yield of pre-donation screening of candidate donors (chapter 5) was low but not zero. The number of travelling donors returning with an acquired infection from abroad (chapters 6-8) was surprisingly low.

It is often questioned whether such labour intensive exercises and precautionary measures, accompanied with high costs and creating anxiety among recipients and donors, are justified. There is no doubt that detection of infection in a recipient through lookback is of benefit for the individual involved (and for his or her contacts because of prevention of secondary transmissions). In addition, active lookback programs give insight in current safety measures and the risk of seroconversion donations. The yield of 5% infected recipients for HIV, HBV or HCV in the Netherlands seems high enough and should be regarded as an argument not to abolish lookback procedures.

Recognizing TTIs at the hospital remains important, but it needs an active haemovigilance surveillance to identify these adverse events. Recognition and confirmation of TTIs is challenging and is complicated by the following aspects:

• Initially TTIs often result in a subclinical or less severe clinical course and therefore may not be recognized. TTIs often are undiagnosed in severely ill transfusion recipients.
• For some infections another transmission route may be more likely (e.g. through mosquito bites or the food chain) and therefore they may go unrecognized as transfusion acquired. Demonstrating a causal association often is complicated, especially in a population with a high general infection pressure.
• Because lookback studies are retrospectively performed, the recipients could have cleared the infection or have died during the delay. The majority of immunocompetent adult HBV infected patients recover spontaneously and clear the virus. Positive antibody screening alone cannot be regarded as evidence of transmission. Genetic analysis of the infectious agent (e.g. the sequencing of HBV DNA) in donor and recipient is the gold standard to confirm or exclude transmission. Pre-transfusion samples of the recipients help to determine seroconversion in recipients, but unfortunately these samples seldom are available.

In the Netherlands a sample of 850 μl plasma of each donation is stored below -20°C during 2 years. These samples are primarily used for additional testing if donors are found to be infected in a following donation. The value of these repository samples is debated because of the high costs of preparing and storage of the approximately 800,000 yearly donation samples, while they are rarely used for the retesting of a pre-seroconversion donation.
An additional issue is that the stored samples often are insufficient for optimal additional testing because of the low volume. Because of the low HBV DNA load in occult HBV donors HBV DNA might not be detected in the small repository sample volume, whereas the blood components transfused contained infectious amounts of HBV. If the repository sample is found negative for an agent, transmission still cannot be excluded completely and a donor triggered lookback should be performed. Hence the value of storage for lookback purposes is limited.

On the other hand, storage of donation material is valuable for research of newly emerging infections, as has been shown during the emergence of Q-fever and hepatitis E virus. The arbitrary storage period of two years is disputable and might be too short for retrospective epidemiological studies.

Since the HIV transmissions in the 80s, blood safety has become a major concern for blood establishments. Additional safety measures are continuously being taken to keep the blood supply safe from potential and established TTIs, often regardless of high costs and a potential threat to the maintenance of the blood supply. Since the introduction of HIV RNA donor screening in the Netherlands 16 years ago, an "HIV RNA only" positive donation did not occur. Knowing that an HIV window period donation may happen any moment, we still believe that HIV RNA testing cannot be abandoned. This approach does not only involve the "classical" TTIs but extends to new potential threats of emerging infectious diseases (EIDs). It seems that any infection through blood is intolerable, while we accept a spectrum of other risks in daily life. If indeed this approach is supported widely, the money that is needed to prevent or find one transmission is a less important factor to take into account.

Assessing the risk of EIDs is challenging. Recognising threats depend on adequate surveillance systems in affected countries. The often limited data of prevalence in the (donor) population and lacking evidence of transmission via transfusion, especially during the beginning of a new outbreak caused by a ‘new’ agent, may result in less reliable blood safety assessments. During a new outbreak, decisions have to be made at short notice. Even when a blood-borne transmission never occurred or was only incidentally reported, blood safety measures are often advised or implemented based on the precautionary principle. Juridical, ethical and political reasons, the anxiety and public commotion, push towards safety measures instead of waiting for more justifiable arguments strengthened by science.

Precautionary blood safety measures are justified while scientific data are still incomplete, or when there is a realistic possibility of serious consequences for the recipients' health. But after implementation of precautionary safety measures, gaining evidence of transmission through blood components and completing the science is complex. In addition, once safety measures have been implemented, withdrawal of safety measures is not easy, and is rarely applied. Currently, for every new outbreak or after a sporadic transfusion accident additional measures are taken as a reflex.

During the last decade blood establishments are more aware of emerging pathogens and their possibility to be transmitted through blood components. A WNV outbreak
in the US, resulting in fatal transmissions through blood; the severe acute respiratory syndrome (SARS) outbreak in China and a large Chikungunya outbreak in Reunion, without evidence of transfusion transmissions, were the first events that caused the deferral of travelling donors in the Netherlands for other reason than malaria. Intensive surveillance and reports of new outbreaks during these years led to additional risk areas for which geographic donor deferral was applied. Finally, after excluding almost all countries outside Europe, a universal 4-week deferral for donors who travelled outside Europe was introduced. This is an example of one safety measure covering several small risks of imported infections.

Next steps that might be considered, include pathogen inactivation of platelets as a pro-active approach; and targeted NAT testing for specific agents in donors who were exposed during travel. Because of the estimated low number of travelling donors returning with an acquired infection abroad, such measures are currently not expected to be cost-efficient.

Large outbreaks do not mean automatically that there is a risk for blood safety. Regarding arbovirus infections, pathogenesis and expression of disease may differ after exposure via transfusion as compared to infection from mosquito bites (e.g. because of absence of promoters in blood as present in mosquito saliva). The infectious dose required for transfusion transmission may be different compared to the natural transmission route, which may explain the low number of transfusion transmitted cases of dengue and chikungunya during high incidence epidemics.

Managing triggers for blood safety measures is a new path we should go into, where the maintenance of safety of blood, the blood supply and the costs should be fairly balanced. The European Up-Front Risk assessment tool (EUFRAT) provides the possibility to estimate the number of expected infections through blood, with or without safety measures, and it could be used as a first assessment before decision making. If indicated, the health benefit measures should ideally be supported by a cost-effective analysis. Until now, several safety measure have been implemented with costs far beyond the normally accepted costs per quality-adjusted life-year (QALY) in health care. High costs per QALY seem to be considered acceptable in the blood transfusion business. The consideration “how safe should blood be” is influenced by societal and philosophical factors, which need to be explored further [1,2].
REFERENCES
