Residual infectious risks in blood transfusion

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ABSTRACT

Background and Objectives
Blood can be infectious if it is donated shortly before infection with hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) becomes detectable. Lookback exercises may detect infection in recipients of pre-seroconversion donations. This study provides an analysis of the Dutch lookback exercises in the years 2000 through 2006.

Materials and Methods
All lookback procedures, triggered by 50 repeat donors seroconverting for HBV (n=32), HCV (n=3), HIV (n=14) and HBV + HIV (n=1), were analysed. Recipients and archived samples of the 96 implicated donations were tested.

Results
For 76 donations, a stored sample was available for HBV, HCV, or HIV PCR testing, revealing two HBV-DNA-positive pre-seroconversion donations. Ninety-three lookback procedures were initiated, to which 91 of 93 hospitals responded. In 87 of 91 cases, the implicated blood product had been administered. In 39 of 87 cases, the recipient was tested, revealing one HIV and two HBV infections. The HIV infection was considered pre-existent. The two HBV-positive patients received components from the donation of which the repository sample tested positive for HBV-DNA. Components of the second HBV-positive pre-seroconversion donation had not been administered.

Conclusion
Among 39 recipients of pre-seroconversion donations, 2 (5%) were found HBV infected by transfusion. The labour-intensive lookback procedures did not reveal any conclusive transmissions additional to the infections detected by PCR testing of repository pre-seroconversion samples.
INTRODUCTION

The selection of blood donors, the serological and nucleic acid-based screening of blood donations and the leucodepletion of blood components decrease the risk of blood-transmitted viral infections. Donor selection will never be perfect. It appeared that at least 25% of Dutch repeat donors who seroconverted had unreported risk behaviour at the time of screening, that would have deferred them from donating blood [1]. Screening tests also have limited sensitivity. Based on test characteristics and the dynamics of infection markers during early infection, the risk in the Netherlands of hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) transmission by window period donations, before the introduction of HBV-DNA screening in 2009, has been calculated to be 1 in 0.2, 12.5 and 5.5 million donations, respectively [2]. Hence, the possibility remains that donors in the very early phase of infection escape detection and infect their recipients [3, 4]. Beside the theoretical calculation of the window period risk, the burden of window period infections can be assessed by the analysis of the lookback procedures among recipients of pre-seroconversion donations.

MATERIALS AND METHODS

Study population

For this study, all Dutch blood donations were included, who were found confirmed positive for HBV, HCV or HIV infection in the period 2000 through 2006, with a history of negative test results in previous donations. In the study period, the routine screening of blood donations involved serological testing for HBsAg, anti-HCV and anti-HIV using the automated Prism system (Abbott Laboratories, Abbott Park, IL); and nucleic acid testing in pools of 48 donations for HIV-RNA and HCV-RNA using the Cobas TaqScreen MPX test on the automated Cobas s201 system (Roche Molecular Systems, Branchburg, NJ). All donations with confirmed infection were reactive in both serological and nucleic acid-based screening; so-called NAT-only donations did not occur.

Confirmatory testing included the serological testing of the index donation and a follow-up sample, for HBV using HBsAg neutralization (Architect; Abbott Laboratories, Abbott Park, IL) and additional HBV serology (Axsym; Abbott Laboratories); for HCV using the Chiron HCV SIA immunoblot assay (Novartis Inc, Emeryville, CA); and for HIV using an HIV-combo assay (Architect; Abbott Laboratories) and the Inno-Lia HIV I/II immunoblot assay (Innogenetics, Ghent, Belgium); plus the detection of HBV-DNA, HCV-RNA or HIV-RNA using Cap-CTM assays (Roche Molecular Systems, Branchburg, NJ).

Following European recommendations [5–7], a lookback procedure was initiated to trace the recipients of all seronegative donations, within the 6 months period previous to (and including) the last seronegative donation preceding an infected donation. The hospitals who received blood components from a pre-seroconversion donation were informed and advised to trace the recipient for testing. Recipients were tested following local labo-
ratory protocols. In addition, the hospitals were asked to provide feedback on the results of recipient tracing and testing.

**Repository samples**

As part of the screening procedure for blood donations, 850 μl plasma of each donation was pipetted using an automated Hamilton Star pipetting station, in 96-deep well plates, for archiving purposes. During 2 years, after a donation, the repository sample was kept in store below -20°C.

If still available, the archived sample of the pre-seroconversion donation was tested using single donation (unpooled) PCR, with the Cobas Amplicor assay for detection of HCV-RNA, HIV-RNA or HBV-DNA (Roche Molecular Systems, Branchburg, NJ).

**Data collection**

The number, timing and nature (HBV, HCV or HIV) of all donor seroconversions in 2000–2006 were retrieved from the records of the quality control department of Sanquin Blood Supply Foundation. Additional information was collected from the blood bank information system; the donor counselling records; and the lookback dossiers of correspondence with the hospitals to which implicated products were distributed. For each seroconversion, the following data were collected: type of infection (HBV, HCV or HIV); date of seroconversion; the number of donations in the 6 months prior to (and including) the last seronegative donation; nature of implicated blood products; repository sample test results; whether lookback was initiated; and the lookback results (i.e. data concerning the recipients: whether they were identified, alive and tested; and subsequent test results).

**RESULTS**

**Implicated components and lookback procedures**

During 2000–2006, 6.25 million whole blood and apheresis donations were collected in the Netherlands. In this period, 69 repeat donors were found to have seroconverted for HBV, HCV or HIV. For 50 of 69 donors, lookback dossiers were available for analysis. The reasons for omitting 19 donors are reported in Table 1. Among the 50 included donors, 32 donors were infected with HBV, 3 donors with HCV, 14 donors with HIV and 1 donor acquired both HBV and HIV. From these 50 donors, 96 potential window period donations and 130 derived components were traced, see Fig. 1. Of the 130 blood components, 121 components were distributed to hospitals and nine components were not issued. Regarding the 121 issued blood components, a lookback procedure was initiated for 93 components. The reasons for not starting a lookback procedure in 28 cases were as follows. Seventeen components were considered not to be at risk because a more recent moment of infection was documented, by confirmatory test results demonstrating acute infection and by supportive information obtained during donor counselling. For 10 components, the negative PCR test result on a repository samples was considered sufficient; and for one component the reason was unknown.
Outcome of lookback procedures

Regarding the 93 lookback procedures, in 91 of 93 cases (98%), the hospitals responded, in two cases, no information was obtained. Among the 91 blood components available for analysis, 87 of 91 were traced as transfused to patients in the hospital; two components were not transfused, and two components could not be traced in the hospital (see Fig. 1).

Of 87 traced transfused patients, 39 (45%) patients were tested for the relevant infection and 48 (55%) patients were not tested. Of the 48 not tested patients, 30 (34%) had died due to the underlying disease, while no signs of HBV, HCV or HIV infection were reported. Twelve (14%) patients were not tested because their physician decided not to do so. In two (2%) cases, the reason for not testing was not recorded, and in four cases, the patient could not be traced.

The screening of recipients

Of the 39 tested patients, 36 (92%) tested negative for the infection under investigation, 3 of 39 (8%) patients tested positive, of which two patients were infected with HBV and one patient with HIV. Both HBV-infected patients received blood components from the same window period donation, of which the repository sample tested positive for HBV by PCR. Genetic comparison of the donor and recipient HBV strains was not performed.

The patient positive for HIV infection was reported by the treating physician as most likely suffering from pre-existent HIV infection, based on the following considerations. Because of clinical suspicion of (non-acute) HIV infection and unaware of the potentially HIV-infected transfusion, the patient was tested for HIV antibodies 27 days after the transfusion. At that time, the patient was found positive for HIV antibodies, with a complete antibody pattern in an anti-HIV immunoblot assay. The CD4-positive cell counts of the patient, respectively, 41, 230 and 251 days after the transfusion, were 240; 80; and 110 CD4+ cells/μl, which like the immunoblot suggests longer existing HIV infection. In addition, the repository sample of the window period donation involved tested negative for HIV-RNA by individual, unpooled PCR. Nevertheless, superinfection with HIV via the window period donation cannot be excluded. Genetic sequencing of the donor and recipient HIV strain was not performed.

Table 1. Reasons for the exclusion of seroconverting donors from lookback.

<table>
<thead>
<tr>
<th>Reason</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of seroconverting donors</td>
<td>69</td>
</tr>
<tr>
<td>Included in analysis</td>
<td>50</td>
</tr>
<tr>
<td>Total excluded from analysis:</td>
<td>19</td>
</tr>
<tr>
<td>Previous donation before 1992 in case of HCV positivity*</td>
<td>4</td>
</tr>
<tr>
<td>Previous donation only used for plasma fractionation</td>
<td>9</td>
</tr>
<tr>
<td>File/data incomplete</td>
<td>6</td>
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</tbody>
</table>

* In the Netherlands blood donor screening for HCV was introduced in 1992, therefore implicated previous donations before 1992 were excluded.
Figure 1. Break-down of 50 seroconverting Dutch repeat blood donors in 2000-2006; of the donations and blood products involved; and of lookback results.
Repository samples
Considering the repository samples of the 96 potential window period donations, for 20 donations, no repository sample was available because the maximum storage time (of 2 years) had been exceeded. Seventy-six repository samples were available for PCR testing: 74 donations were negative; two donations were positive for HBV-DNA, originating from two different donors. Both blood components (red cell concentrate and platelet concentrate) from one HBV-positive window donation were delivered to hospitals. Both components were transfused and the two patients were found to be HBV infected, as described in the previous paragraph. The components (fresh-frozen plasmas) from the other HBV positive window period donation were still in the inventory and have been withdrawn in time.

DISCUSSION
The detection of 69 seroconversions among Dutch repeat blood donors triggered labour-intensive lookback procedures. Two patients were traced who most likely acquired HBV infection from a single donation in the window period. One recipient of a potential HIV-positive window period donation tested positive for HIV, but most likely the HIV infection in this patient was pre-existent. Unfortunately, at that time, genetic sequencing of the donor and recipient strains was not part of the lookback procedure, and therefore the transmission of HIV cannot be excluded or confirmed on phylogenetic grounds.

Donors who tested positive for HCV, with the previous donation donated before 1992, were excluded from the study. These donors would have been found positive in prior donations if anti-HCV testing would have been available, while this study concerns window period donations. The interests of the recipients of the excluded HCV-infected donations were not ignored. Apart from this study, the recipients were traced and tested, as published by Vrielink et al [8].

The detection of HBV transmission by lookback is in line with the theoretical risk of HBV, HCV and HIV window period infection. The window period of HBV and the incidence of HBV among Dutch repeat blood donors exceed those of HCV and HIV [2, 9]. Nevertheless, even for HBV, the yield of the lookback exercises was limited. One factor that possibly influences the low yield is that only part of the recipients was investigated. For 40% (48/121) of the implicated blood components, the recipients were not tested, mainly because the physician decided so or the patient had died. In our study, 34% of the implicated patients had deceased, which is comparable with survival rates in literature [10, 11]. For 28% (34/121) of the implicated blood components, the recipients were not traced, mainly because a lookback procedure was considered unnecessary. For 32% (39/121) of the distributed blood products, the recipients were tested for infection. To enable comparison with two other lookback studies, the number of transfused components must be considered. In this study, for 87 of 121 distributed blood components, actual transfusion was reported and 39 of 87 (45%) of the recipients have been tested. This is comparable with an HIV lookback study in England and Wales, where 51 recipients of 116 transfused
components (44%) were tested [12]; and with a Canadian hepatitis C lookback exercise, where 160 recipients of 494 transfused components (32%) were tested [13]. Regarding HBV, an additional minor reason for finding few transmissions may be that recipients were immune for HBV, due to vaccination or previous HBV infection. The HBV immune status of the recipients in this study is unknown, and population-based estimators are not available.

For 20 of 96 (21%) potential window period donations, no repository sample was available because the arbitrary storage time of 2 years had been exceeded. A longer storage time would have decreased this proportion, with decreasing yield and with increasing costs. A negative PCR test result on a repository sample decreases the likelihood of transmission, but a residual risk remains [14]. In the EU, the tracing of potential window period donations is mandatory. In our study, the positive HBV-DNA test result in a repository sample correlated with the positive HBV lookback result in the two recipients. In a recent report on 113 British donors seroconverting for HIV, the positive HIV-RNA test result in an archived pre-seroconversion sample correlated with the finding of an infected recipient via lookback [12]. In both studies, the tracing and testing of recipients did not reveal additional infections. It appears that the tracing and testing of recipients adds little to the testing of repository pre-seroconversion samples.
REFERENCES