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# Re-assessing the risk of undetected HBV, HCV and HIV in deceased tissue and living surgical bone donors in England

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**Abstract** Testing of living surgical bone and deceased tissue donors by NHS Blood and Transplant (NHSBT) has included individual donation (ID) nucleic acid testing (NAT) for HBV, HCV and HIV since 2008. Here, the well-established window period methodology was used to estimate residual risk (RR). Prevalence of viral markers was calculated among both tissue donor populations. Incidence was derived by adjusting incidence among new blood donors by the prevalence ratio for tissue and new blood donors. Residual risk (RR) was calculated as the product of incidence and duration of WP for single donor HBV NAT at 0.058 years (21 days), HCV NAT at 0.008 years (3 days) and HIV NAT at 0.014 (5 days). Between 2013 and 2017, 7886 living surgical bone donors were tested, 16 were positive for markers of HBV, HCV and HIV. HCV had the highest prevalence at 114/100,000 donors. Incidence and RR was highest for HBV at 3.55/100,000-person years and 0.32/100,000 donors (95% CI 0.11/100,000–1.42/100,000). Among 9751 deceased tissue donors tested, 22 were positive for viral markers. HBV had highest prevalence at 174/100,000 donors, and the highest incidence and RR at 8.12/100,000 person years and 0.74/100,000 donors (95% CI 0.08/100,000–2.99/100,000). Using ID NAT, RR of not detecting a HBV, HCV and HIV WP donation among tissue donors is less than 1/100,000 donors. These estimates provide a good starting point for discussing potential risks of viral transmission through tissue transplant with patients.

**Keywords** Deceased tissue donors · Living tissue donors · Residual risk

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## Introduction

Human tissue allografts have been used for several years in transplantation to repair or replace diseased or damaged tissues. The key advantage of human allografts is that they have properties of native tissue that cannot be replicated by prosthetic or biological grafts. Most of the tissue allografts are donated by deceased tissue donors, with living donors donating femoral

head when undergoing a primary hip replacement procedure. Transmission of viral infections through tissue transplantation are rare but have been documented (Locasciulli et al. 1995; Eastlund 1995; Hoft et al. 1997; Hinsenkamp et al. 2012; CDC 2003). These generally occurred many years ago in minimally processed tissues, mostly before the advent of highly sensitive serology testing protocols and all prior to the implementation of nucleic acid testing (NAT). However, in the absence of a surveillance system for these transmissions there is possible underacertainment in reporting.

The NHS Blood and Transplant (NHSBT) facility in Liverpool England hosts one of the largest multi-tissue banks in Europe. Donation is voluntary and non-remunerated. The information on medical and social history required for donor evaluation and consent is obtained directly from the living donors. Family members of deceased donors provide consent and medical history. Medical and social history is gathered with a standard questionnaire to identify and exclude those donors at higher risk of blood-borne infection. Although donor selection criteria are similar to that of blood donors, the risk exposures that would exclude the donor might be unknown to the family members. To minimise this risk, additional information is gathered from the clinical team if the donor died in a hospital, general practitioners and autopsy reports if performed.

NHSBT tissue donors are tested to the same protocol as blood donors for hepatitis B surface antigen (HBsAg), antibodies to hepatitis C (anti-HCV), combined antibodies/antigen to human immunodeficiency virus (HIV) types 1 and 2 (anti-HIV), treponemal antibodies (syphilis) and antibodies to human T-lymphotropic virus (HTLV) types 1 and 2 (anti-HTLV). In addition, anti-HBc and NAT for HBV, HCV, HIV are mandatory tests for tissue donors, with NAT tests performed in individual samples and not pooled. Donations are processed and released if they meet the quality standards and all the mandatory test results are negative. Data on tissue donors tested by NHSBT are collated by the NHSBT and Public Health England (NHSBT/PHE) epidemiology unit for the surveillance programme, which includes data on blood donors through a parallel scheme (Reynolds, Davison, and Brailsford 2019).

On very rare occasions a false negative test result may arise if a donation is made during the window period, i.e. the time after infection when there is enough virus to be potentially transmitted but not be detected by the assay in use. The rate of non-detection is estimated as the residual risk (RR) and expressed per 100,000 donors tested. Deceased tissue donors can donate many types of tissues such as skin, tendons corneas and cardiovascular grafts and thereby an undetected infection could have the potential to transmit infections to many recipients. Bone from living and deceased donors is irradiated to minimise onwards transmission of undetected viral infections.

RR estimates help to inform polices and practice regarding tissue safety. For English tissue donors, these were first estimated for donations made during 2001–2006. At that time, testing was for serological markers only and a follow up sample was required before a product could be released as negative on testing. Calculations were limited to living surgical bone donors because of an absence of data about deceased tissue donors. RRs for testing of initial samples were higher for surgical bone donors than new blood donors but reduced to negligible levels for follow up samples.

In 2007, NAT testing of samples from deceased tissue donors was introduced to minimise WP risk. This replaced the need for a follow up sample in living tissue donors 2008. In 2012, NHSBT/PHE surveillance programme expanded to include data for deceased tissue donors who gave corneas from two major eye banks in Bristol and Manchester. These eye banks subsequently merged with NHSBT Tissue Services in April 2015. Given these changes, it was important to update estimates to inform current and future tissue donation policies. In this paper, the prevalence of observed HBV, HCV and HIV among both living surgical bone and deceased tissue donors is estimated. The data were used alongside new blood donor data to calculate incidence and RR of NOT detecting markers due to WP of the assays for tissue donors tested by NHSBT during 2013–2017. The method was adapted from those previously published for blood, tissue and organ donors in the UK (Brant and Davison 2008, 2009; Davison et al. 2019; Soldan et al. 2005).

## Methods

### Data sources

Data on the number of deceased tissue donors, living bone donors and new and repeat blood donors tested and confirmed positive for makers of HBV, HCV and HIV by NHSBT between 2013 and 2017 were extracted from NHSBT/PHE Epidemiology Unit surveillance database.

### Estimating prevalence, incidence and residual risk

Prevalence and incidence of confirmed markers was estimated for the two tissue donor populations and the new blood donors by gender and donor age groups less than 50 years and 50 years plus as previously described.(Brant and Davison 2008) In brief, prevalence per 100,000 donors was calculated by dividing the number of confirmed positive by the number tested for each donor group. Incidence in tissue donors was not be directly estimated as seroconversion is generally not detected in that group. Instead, it was estimated as the incidence among new blood donors per 100,000 person years multiplied by the ratio of the prevalence for each virus among the tissue donor groups to the prevalence of the virus among new blood donors. Incidence among new blood donors was estimated as the observed incidence in repeat blood donors adjusted by factor Z to account for differences in the rates of newly acquired infections among new and repeat blood donors derived from blood donor surveillance data. Factor Z for each virus was provided by the NHSBT/PHE Epidemiology Unit. Incidence in repeat blood donors was calculated as the number of observed seroconversions within 1-year of the previous negative donation or other microbiological and/or clinical evidence of recently acquired infection divided by the number of person years (Soldan et al. 2003).

RR for living surgical bone and deceased tissue donors was calculated as the product of incidence and duration of WP for single donor HBV NAT at 0.058 years (21 days), HCV NAT at 0.008 years (3 days) and HIV NAT at 0.014 (5 days) for each gender and age group strata. These values were weighted by the proportion of donors in each stratum and summed to give an overall estimate for both tissue donor groups.

95% confidence intervals (95% CI) for RR were calculated by simulation using STATA 15 as previously described for organ donors.(Davison et al. 2019) Incidence and RR for each strata was calculated 1000 times using different parameter values sampled from a defined statistical distribution to reflect the uncertainty and the 2.5 and 97.5 percentile of the output variables as the upper and lower values of the 95% CI.

## Results

### Living surgical bone donors

Over five years, NHSBT tested 7886 living surgical bone donors and 16 had confirmed markers of HBV, HCV or HIV (Table 1). Markers of HCV were the most common (9) and approximated to a prevalence of 114/100,000 donors. Overall, most donors with confirmed markers were males aged 50 plus years, with only HCV identified in donors < 50 years. No donors had evidence of recently acquired infection.

The prevalence of confirmed viral markers estimated in living surgical bone donors exceeded prevalence estimated in new blood donors (Table 2). The overall prevalence ratio was highest for HCV at approximately 5:1, this increased to over 33:1 among female donors aged < 50 years.

Estimated incidence and RR was highest for HBV at 3.55/100,000-person years and 0.32/100,000 donors (95% CI 0.11/100,000–1.42/100,000) (Table 2). HBV incidence among living surgical bone donors was almost twice that of HCV and 10-times that of HIV. HBV RR among living surgical bone donors was 25-times greater than for HCV and 100-times for HIV.

### Deceased surgical bone

Of the 9751 deceased tissue donors tested, 22 were confirmed with markers of HBV, HCV or HIV (Table 1). The most common was for HBV accounting for 17 donors with an estimated prevalence of 174/100,000 donors. Only one deceased tissue donor had confirmed markers of HIV. No positive donors had evidence of recently acquired infection. All deceased tissue donors with confirmed viral markers were 50 plus years.

The prevalence of confirmed viral markers deceased tissue donors exceeded prevalence estimated

**Table 1** Number and prevalence rate of confirmed markers of HBV, HCV and HIV among living surgical bone, deceased tissue and new blood donors by age group and gender

| | | Age group | Tested | HBV[1] | | HCV | | HIV | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | *n* | per 100,000 | *n* | per 100,000 | *n* | per 100,000 |
| Living surgical bone | Females | <50 | 250 | 0 | – | 1 | 400.00 | 0 | – |
| | | 50+ | 4159 | 3 | 72.13 | 2 | 48.09 | 1 | 24.04 |
| | Males | <50 | 217 | 0 | – | 1 | 460.83 | 0 | – |
| | | 50+ | 3260 | 3 | 92.02 | 5 | 153.37 | 0 | – |
| | | **All** | **7886** | **6** | **76.08** | **9** | **114.13** | **1** | **12.68** |
| Deceased | Females | <50 | 532 | 0 | – | 0 | – | 0 | – |
| | | 50+ | 3353 | 6 | 178.94 | 1 | 29.82 | 0 | – |
| | Males | <50 | 754 | 0 | – | 0 | – | 0 | – |
| | | 50+ | 5112 | 11 | 215.18 | 3 | 58.69 | 1 | 19.56 |
| | | **All** | **9751** | **17** | **174.34** | **4** | **41.02** | **1** | **10.26** |
| New blood donors | Females | <50 | 400339 | 69 | 17.24 | 48 | 11.99 | 10 | 2.50 |
| | | 50+ | 44362 | 6 | 13.53 | 26 | 58.61 | 2 | 4.51 |
| | Males | <50 | 251978 | 187 | 74.21 | 77 | 30.56 | 10 | 3.97 |
| | | 50+ | 35993 | 17 | 47.23 | 18 | 50.01 | 1 | 2.78 |
| | | **All** | **732672** | **279** | **38.08** | **169** | **23.07** | **23** | **3.14** |

[1]HBV excludes anti-HBc only

in new blood donors (Table 2). For deceased tissue donors, the overall ratio was highest for HBV at 5:1, increasing to 13:1 in females aged 50 years plus.

Estimated incidence and RR was highest for HBV for deceased tissue donors at 8.12/100,000 person years and 0.74/100,000 donors (95% CI 0.08/100,000–2.99/100,000) respectively (Table 2). HBV incidence was 12-times and 29-times that of HCV and HIV. HBV RR was over 200-times greater than either virus among the deceased group.

## Conclusion

For the first time, we have estimated the RR of not detecting a potentially infectious HBV, HCV or HIV WP donation among deceased tissue donors in England and re-estimated RR for living surgical bone donors in the presence of NAT testing. For both tissue donor groups tested by NHSBT between 2013 and 2017 the estimated RRs were below 1/100,000 donors, with HBV being the virus most likely to not be detected on testing. For living surgical bone donors, the highest observed prevalence overall was for HCV at 114.13/100,000 donors. However, the highest incidence was estimated for HBV at 3.55/100,000 donors and in combination with the longest duration of window period of all the assays (21 days for HBV NAT) this gave rise to the highest RR at 0.32/100,000 donors. For deceased tissue donors, HBV was found to have the highest prevalence at 174/100,000 donors, highest incidence at 8.12/100,000 donors and highest RR at 0.74/100,000 donors.

The RR values estimated here among tissue donors were higher than estimated for new blood donors at 0.14/100,000 donors for HBV and 0.01/100,000 donors for HCV, and similar at 0.002/100,000 blood donors for HIV in the UK during 2015–2017. Estimates in tissue donors were up to almost sixfold higher for HBV among deceased tissue donors. The increased RR is despite the shorter WP of single NAT testing used for tissue donors than the pooled sample testing carried out for blood donations, and is due to the higher prevalence of infections in tissue donors than the new blood donors, even though donor selection criteria are very similar. For HBV, the prevalence ratio between tissue and new blood donors was greater than one and gave rise to an increased estimated incidence and RR. However, for HCV and HIV although the overall prevalence ratio was greater

**Table 2** Parameters for and estimates of HBV, HCV and HIV residual risk with 95% confidence intervals in living surgical bone and deceased donors, NHSBT 2013–2017

| Donor type | Gender | Age group | HBV | | | | HCV | | | | HIV | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Prevalance ratio (tissue to new donors) | Incidence new blood donors per 100,000 PYRS | Incidence tissue blood donors per 100,000 PYRS | Risk per 100,000 tissue donors (95% CI) | Prevalance ratio (tissue to new donors) | Incidence new blood donors per 100,000 PYRS | Incidence tissue blood donors per 100,000 PYRS | Risk per 100,000 tissue donors (95% CI) | Prevalance ratio (tissue to new donors) | Incidence new blood donors per 100,000 PYRS | Incidence tissue blood donors per 100,000 PYRS | Risk per 100,000 tissue donors (95% CI) |
| Living surgical bone | Females | <50 | 0.00 | 2.18 | 0 | 0.00 | 33.36 | 0.83 | 27.61 | 0.23 | 0.00 | 0.04 | 0.00 | 0.00 |
| | | 50+ | 5.33 | 0.93 | 4.95 | 0.28 | 0.82 | 0.00 | 0.00 | 0.00 | 5.33 | 0.05 | 0.26 | 0.004 |
| | Males | <50 | 0.00 | 0.00 | 0.00 | 0.00 | 15.08 | 0.00 | 0.00 | 0.00 | 0.00 | 0.22 | 0.00 | 0.00 |
| | | 50+ | 1.95 | 3.63 | 7.07 | 0.41 | 3.07 | 0.52 | 1.59 | 0.01 | 0.00 | 0.07 | 0.00 | 0.00 |
| | | **All** | 2.00 | 1.77 | 3.55 | **0.32 (0.11–1.42)** | 4.95 | **0.38** | 1.88 | **0.01 (0.00–0.19)** | 4.04 | **0.09** | 0.35 | **0.002 (0.00 - 0.029)** |
| Deceased | Females | <50 | 0.00 | 2.18 | 0.00 | 0.00 | 0.00 | 0.83 | 0.00 | 0.00 | 0.00 | 0.04 | 0.00 | 0.00 |
| | | 50+ | 13.23 | 0.93 | 12.29 | 0.71 | 0.51 | 0.00 | 0.00 | 0.00 | 0.00 | 0.05 | 0.00 | 0.00 |
| | Males | <50 | 0.00 | 0.00 | 1.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.00 | 0.22 | 0.00 | 0.00 |
| | | 50+ | 4.56 | 3.63 | 16.53 | 0.95 | 1.17 | 0.52 | 0.61 | 0.005 | 7.04 | 0.07 | 0.50 | 0.01 |
| | | **All** | 4.58 | 1.77 | 8.12 | **0.74 (0.08–2.99)** | 1.78 | 0.38 | 0.57 | **0.003 (0.000–0.032)** | 3.27 | **0.09** | 0.28 | **0.004 (0.000 - 0.015)** |

than one, the estimated RR in tissue donors was similar or less than new blood donors. This relates to the very low number of HCV or HIV among donors which gave rise to zero incidence in some age group strata.

Despite the overall higher RR in tissue donors than new blood donors, there are far fewer tissue donations made each year and it is therefore less likely in any given year that we could expect to not detect a WP donation. Extrapolating the value of RR estimated here to the 629 surgical bone donors tested by NHSBT in 2017, it could be up an estimated 500 years before one HBV WP donation may not be detected. Similarly, based on 3329 deceased tissue donors tested in 2017, it could be up to 41 years before one HBV WP donation is not be detected in this donor group.

The calculations of RR among tissue donors made here rely on the assumption that the difference in incidence between the blood and tissue donors is in the same direction and proportion as the difference in observed prevalence, which may not be the case. Also, an adjustment is made to account for some of the difference in prevalence between the blood and tissue donors by gender and age group; the purpose of the adjustment is to improve the estimate of prevalence ratio, the very low number of positive donors gave rise to zero values in some gender/age group strata and increased the uncertainty overall with broad 95% CI, ranging from zero up to 20-fold greater than the point estimate for HCV RR in living surgical bone donors.

A further limitation is that these estimates of RR are modelled for non-detection of viral markers in the blood sample from the donor and do not relate to potential infectious risk in the donated tissue. This is difficult to factor into this type of assessment because it will vary by type of tissues and the method of processing which includes further risk mitigation with different types of disinfection and sterilisation steps.

To conclude, in England there is a very low prevalence of HBV, HCV and HIV observed among tissue donors, and incidence is estimated to be low. In the presence of ID NAT, the RR of not detecting a window period infection is low and given the very small number of donors tested each year, it is anticipated that it would be many years before a potentially infectious sample was not detected. These estimates provide a good starting point for discussion with the patients, assuming all tissue types have similar risk profile, in explaining the risk of viral transmission through tissue transplant. This is a valuable tool for the surgeons to explain the benefits of treatment, available alternatives that can be considered against the albeit small risk, of transmissible infections through tissue allografts to obtain fully informed consent from the recipients for the procedure.

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**Availability of data and material** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

**Declarations**

**Conflict of interest** The authors have no conflicts of interest.

**Consent for publication** Appropriate approval has been given by Public Health England.

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