TITLE: Probability of not receiving testing in a national lookback programme: the English experience.

AUTHORS: The English National Blood Service HCV Lookback Collation Collaborators (*see appendix)

INSTITUTION: National Blood Service (NBS), England

DISCLAIMERS: None

AUTHOR FOR CORRESPONDENCE: Kate Soldan, PHLS CDSC, GRO-C GRO-C, UK, Tel: + (0) GRO-C, Fax: +(0 GRO-C, Email: ksoldan@ GRO-C

REPRINT REQUESTS: Dr Angela Robinson, Medical Director, National Blood Authority, Oak House, Reeds Crescent, Watford, Herts, WD1 1QH

SOURCE OF SUPPORT: None.

RUNNING HEAD: Probability of testing in a lookback

Abstract

BACKGROUND: The HCV lookback programme was designed to trace and offer testing to recipients transfused with blood components from donors subsequently found to be anti-HCV positive. 88% of components entering lookback did not result in a tested recipient.

STUDY DESIGN AND METHODS: Data from English blood centres was collated in order to describe the outcomes of the HCV lookback programme. The data were used to assess factors effecting the likelihood that recipients of lookback components received testing.

RESULTS:

4,424 recipients of 9,222 blood components were identified. 1,351 blood recipients were reported as having been traced for testing. The fate of 23% (2,119) of components was not identified due to inability to access information from records. Sixty-one percent (2,711) of identified recipients were known to be dead at the time of tracing. Fifteen percent (651) were not tested due to other reasons. Factors positively associated with receiving testing in identified recipients were younger age at transfusion, more recent year of transfusion, certain component types and transfusion under the care of certain medical specialities: these effects were largely explained by the association of these factors with post-transfusion survival.

CONCLUSIONS: Not-testing was largely due to death prior to the lookback and partly due to inability to access information from records and to decisions to not test. The probability of testing was associated with several factors that could be used to focus the efforts of similar lookbacks in the future.

KEYWORDS: transfusion, HCV, lookback, blood recipients, mortality

INTRODUCTION

The rationale, methods and outcomes of the HCV lookback in England has been described elsewhere[1]. The outcome in terms of yield of tested recipients, and infections diagnosed, for the effort required per component entering lookback was low compared to many other infection screening programmes, but within the range for published HCV lookbacks. This paper presents an analysis of factors associated with receiving testing.

MATERIALS AND METHODS

Data about donors, components and recipients were linked and collated into a national dataset[1]. Logistic regression models (using STATA 6.0) were used to estimate the odds ratios of the lookback procedure for any component resulting in the testing of a recipient. Univariable and multivariable analyses where performed to investigate the effects of the following variables: recipient's age at time of transfusion, recipient's sex, year of transfusion, time between transfusion and testing, component type transfused and medical speciality of the clinician prescribing the transfusion.
The odds of death after transfusion and before the lookback were investigated similarly.

Chi-squared tests were used to test the statistical significance of differences between proportions. T-tests and Kruskal-Wallis tests were used, as appropriate, to test the statistical significance of differences between distributions of continuous variables. Statistically significant results were taken as those with a probability of less than 0.05.

RESULTS

The fate of 33% (2,119/9,222) of the components reported to the national dataset was not identified. For those known to have been transfused, recipients were not identified for 3% (154/4,586). Sixty-one percent (2,711) of identified, transfused recipients were known to be dead and 15% (651) did not proceed for testing either because they were not traced or because their clinician indicated they were unsuitable for testing (which reason applied for each case is not known). 76% (3,362) of identified recipients were not tested. Overall, for every 100 components entering lookback, 20 living recipients were identified, and 6 HCV infections were found.

Figure 1 shows the numbers of lookback components, recipients identified, recipients not known dead and recipients tested by year of donation.

Table 1 shows the reported fate of the 9,222 lookback components included in the lookback dataset.

Figure 1: Dataset: Components and recipients by year of donation

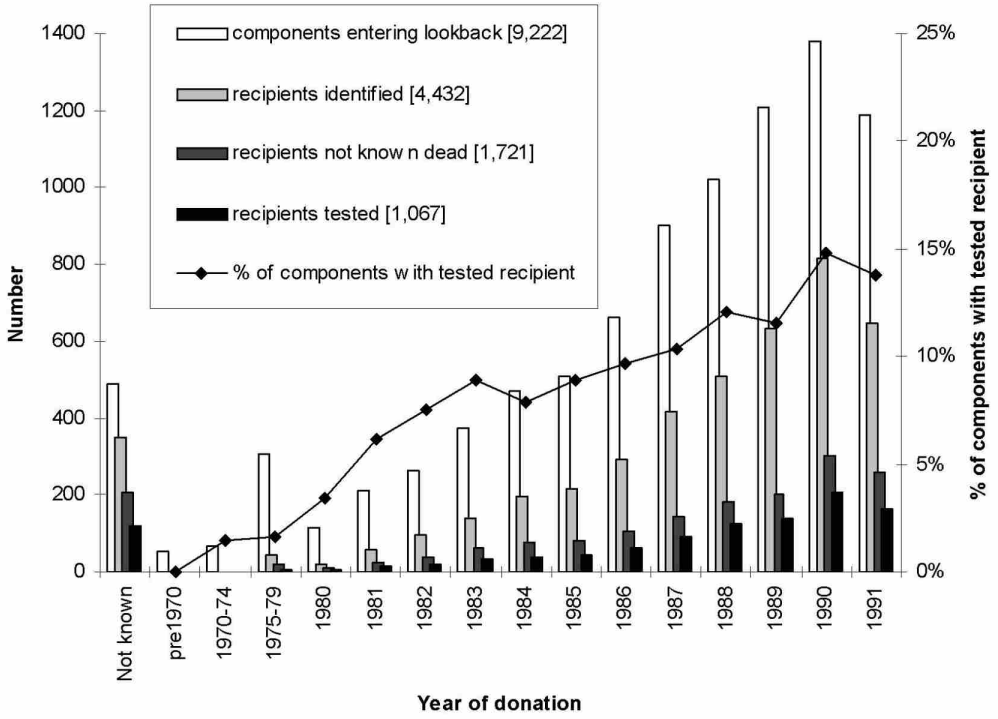

Table 1: Lookback dataset: Number and fate of lookback components and outcome of lookback for transfused components.

Table 1: National dataset: Number and fate of lookback components and outcome of lookback for transfused components.

Fate of component	Fate of recipient	Whole blood		Red cells		FFP & cryo		Platelets		Not known		Total	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Transfused		939	59%	2468	64%	305	14%	844	66%	24	6%	4580	50%
Not tested		*679*	*42%*	*1868*	*49%*	*235*	*11%*	*717*	*56%*	*14*	*4%*	*3513*	*38%*
	- died	486	30%	1391	36%	190	9%	640	50%	10	3%	2717	29%
	- identified but not tested	181	11%	354	9%	40	2%	69	5%	4	1%	648	7%
	- not identified	12	1%	123	3%	5	0%	8	1%	0	0%	148	2%
Tested		*260*	*16%*	*600*	*16%*	*70*	*2%*	*127*	*10%*	*10*	*3%*	*1067*	*12%*
To BPL[1]	-	6	0%	1	0%	1401	66%	0	0%	3	1%	1411	15%
Discarded[2]	-	222	14%	443	12%	224	11%	176	14%	59	16%	1124	12%
Not identified	-	438	27%	923	24%	192	9%	267	21%	287	77%	2107	23%
Total		*1605*	100%	*3835*	100%	*2122*	100%	*1287*	100%	*373*	100%	*9222*	100%
		17%		42%		23%		14%		4%		100%	

1. BPL = BioProducts Laboratory, for plasma fractionation
2. Includes donations issued for quality assurance, laboratory use and research.

For 48 (2.3%) of the untraced components the fate of the component was reported as “transferred” (i.e. to another blood centre for issue) but the component was not reported by any other centre contributing to the national dataset. 18 (1%) were reported as “returned to the blood centre” with no records of re-issue and had probably been discarded. For the remaining untraced components information about the fate of the component was not available: it was not reported whether information was unavailable at centres or at hospitals.

The age and sex of the 4,424 identified recipients included in the lookback dataset, sub-grouped by testing status, is summarised in Table 2.

The odds ratios for lookback at transfused components resulting in undergoing testing, for various recipient and donor variables are shown in Table 3.

Table 2: National dataset: Number and fate of lookback components and findings for recipients of transfused components. Comparisons of variable found significantly different (at 5% significance level) are shown in **bold**[1].

Recipients [number]	**% female**	**Age (yrs) at time of transfusion**	**Age (yrs) at time of tracing**	**Time (yrs) between transfusion and testing[2]**
	[number with data available] (Standard deviation of mean)			
Identified [4,424]	48% [4,047]	median: 60 mean: 55 [3,746] (23.0)	median: 68 mean: 62 [3,784] (22.9)	NA
Tested [1,086]	51% [1,066]	median: 45 mean: 43 [1,075] (21.5)	median: 52 mean: 50 [1,080] (21.3)	median: 6.8 mean: 7.6 [440] (2.8)
Not tested	46% [2,981]	median: 66 mean: 60 [2,671] (21.6)	median: 73 mean: 67 [2,704] (21.7)	NA
Tested-not known dead [951]	51% [1,049]	median: 44 mean: 42 [1,061] (21.5)	median: 51 mean: 50 [1,066] (21.2)	median: 6.8 mean: 7.6 [435] (2.8)
Not tested-not known dead	55% [686]	median: 65 mean: 58 [609] (23.2)	median: 72 mean: 65 [614] (23.1)	NA[3]
Comparison: not known dead tested vs not tested	*p = 0.71*	***p < 0.001***	***p < 0.001***	*NA*

[1] p value for comparison of age and time variables = result of Kruskal-Wallis rank test. T-tests were also performed, with similar results.

[2] Excluding those known positive at the time of tracing.

[3] Untested identified recipients had been transfused 4.3 to 21 years (mean 7.9 years, SD 2.9, median 7 years) prior to the median specimen date for the tested recipients.

Table 3: Lookback dataset logistic regression results: effects of recipient and donor variables on the likelihood of testing transfused recipient. Variables with significant effect on the model (at 5% significance level) shown with p value in **bold**.

Variable	No. of obs.	p~	Odds of testing if transfused (95%CI)	No. of Obs.	p~ value	Odds of testing if transfused (95% CI)
			Univariable	2,478		*Multivariable*
Female	4,047	**0.01***	1.20(1.04-1.38)		1.00	1.05(0.86-1.29)
Age at transfusion (yrs)	3,744	**<.01***	0.97(0.96-0.97)		**<.01***	0.96(0.95-0.96)
Year of transfusion	4,204	**0.04***	1.04(1.01-1.07)		0.95	1.06(1.02-1.10)
Period of donation	4,204	**0.02***				
1990 or later			1.0(baseline)			-
1985-1989			0.86(0.73-1.00)			-
1980-1984			0.75(0.59-0.95)			-
pre-1980			0.44(0.18-1.04)			-
Component type	4,556	**<.01**			0.80	
red cells			1.0(baseline)			1.0(baseline)
whole blood			1.18(0.99-1.39)			1.02(0.81-1.30)
platelets			0.55(0.45-0.68)			0.66(0.48-0.91)
plasma/cryo			0.96(0.73-1.27)			0.63(0.43-0.91)
Speciality	2,852	**<.01***			**<.01***	
cardiothoracic			1.0(baseline)			1.0(baseline)
care of elderly			0.03(0.01-0.14)			0.02(0.00-0.17)
gastroenterology			0.83(0.49-1.40)			0.63(0.35-1.16)
haematology			0.42(0.31-0.57)			0.30(0.20-0.44)
medicine			0.41(0.28-0.61)			0.42(0.27-0.64)
obs/gynae			3.66(2.48-5.40)			1.44(0.89-2.31)
orthopaedics			1.05(0.76-1.45)			1.17(0.79-1.72)
paediatrics			2.07(1.25-3.44)			0.23 (0.12-0.44)
oncology/radio.			0.12(0.06-0.24)			0.07 (0.03-0.14)
surgery			0.63(0.47-0.85)			0.62 (0.44-0.88)
urology			0.56(0.34-0.92)			0.78 (0.45-1.34)
other			0.67(0.41-1.10)			0.50(0.28-0.89)

NA = not applicable. NE = not estimated: too few observations to calculate. p~ = probability of the observed difference in deviance between the models with and without the variable. * = Factors significant when identified recipients who were known to be dead were excluded. $^{>}$ = An interaction was observed with the effect of age at transfusion on the odds of testing differing for recipients of different component types.

No donor factors (year born, PCR status, sex) had an effect on the probability of recipient testing.

Unknown fate of a unit was significantly associated with earlier year of donation [Odds ratio of fate being unknown for year of donation 0.79 (0.78-0.81). OR for period of donation; 1990 or later 1.0 (baseline), 1985-1989: 2.02 (1.75-2.34), 1980-1984: 5.31 (4.52-6.25), pre-1980: 26.50 (20.53-34.22)].

Risk of death prior to testing

The most common reason for identified recipients not receiving HCV testing was death prior to testing. The odds of death prior to testing associated with recipient and donor variables are shown in Table 4. When the analyses shown in Table 3 of the effects of the recipient and donor variables on the likelihood of testing were re-run for recipients not known to be dead, age at transfusion [OR 0.97 (0.96-0.97)], year of transfusion [OR 1.10 (1.06-1.14)], and speciality at the time of transfusion remained significant associated with testing in univariable analyses. Age at transfusion [OR 0.97 (0.96-0.98)] and the speciality at time of transfusion were significant in the multivariable recipient analyses after excluding those known to be dead. The predictive value of component type on whether testing was performed was completely explained by the risk of known death associated with those component types. This suggests that the risk of death associated with certain component types is a risk of early death in hospital - as the effect is fully explained by mortality recorded in hospital notes. The risk of death (assumed to largely account for not being tested) associated with other variables continues acting once the recipient is discharged from hospital care.

Table 4: Lookback dataset logistic regression results: effects of recipient and donor variables on the likelihood of death of transfusion recipients prior to lookback. Variables with significant effect on the model (at 5% significance level) shown with p value in **bold**.

Variable	No. of Obs.	p~ value	Odds of recipient death before lookback (95% CI)	No. of Obs.	p~ value	Odds of recipient death before lookback (95% CI)
			Univariable	2,461		*Multivariable*
Female gender	3,7889	**<.01**	0.67(0.59-0.77)		0.98	0.77(0.63-0.93)
Age at transfusion (yrs)	3,555	**<.01**	1.03(1.02-1.03)		**<.01**	1.04(1.04-1.05)
Year of transfusion (yrs)	3,986	0.61	0.99(0.97-1.02)		0.97	0.95(0.92-0.98)
Period of donation	3,986	0.15				
1990 or later			1.0(baseline)			-
1985-1989			1.18(1.03-1.36)			-
1980-1984			1.08(0.87-1.35)			-
pre-1980			1.03(0.53-2.01)			-
Component type	4,145	**<.01**			0.36	
red cells			1.0(baseline)			1.0(baseline)
whole blood			0.69(0.59-0.81)			0.99(0.79-1.26)
platelets			2.08(1.72-2.52)			1.85(1.36-2.51)
plasma/cryo			1.03(0.80-1.33)			1.44(1.02-2.05)
Speciality of transfusion	2,832	**<.01**			**<.01**	
cardiothoracic			1.0(baseline)			1.0(baseline)
care of elderly			5.06(2.86-8.97)			2.83(1.50-5.37)
gastroenterology			1.08(0.65-1.81)			1.17(0.64-2.11)
haematology			3.40(2.51-4.59)			4.15(2.83-6.10)
medicine			2.50(1.75-3.56)			2.30(1.53-3.45)
obs/gynae			0.20(0.13-0.32)			0.52(0.30-0.89)
orthopaedics			0.69(0.50-0.97)			0.55(0.37-0.81)
paediatrics			0.71(0.42-1.20)			5.59(2.91-10.77)
oncology/radio.			8.90(5.13-15.43)			15.9(8.19-30.86)
surgery			1.72(1.29-2.30)			1.60(1.14-2.24)
urology			1.85(1.17-2.92)			1.13(0.68-1.89)
other			1.33(0.83-2.13)			1.69(0.96-2.97)

p~ = probability of the observed difference in deviance between the models with and without the variable.

Amongst 873 recipients for whom year of death was reported, the interval between year of transfusion and year of death was less than 1 for 47%, 1 for 23%, 2 for 10%, 3 for 4% 4 for 5%, 5 for 3%, 6-10 for 7% and over 10 for 1%.

Some free text about the cause of death was reported for 46% (1,199) of those known to be have died. Of these, 5% mentioned liver related conditions, 38% attributed death to haematological conditions, 19% to malignancies, 11% to cardiac and peripheral vascular conditions, 3% to cerebral vascular problems, 7% to respiratory conditions, 4% to infectious causes, 4% to gastrointestinal conditions and 7% to various other conditions.

DISCUSSION

Overall, approximately 1 living recipient was identified per 5 components entering lookback, and 1 infected recipient was identified per 16 components entering lookback, per 8 recipients identified and per 2 tests performed, increasing to 1 per 12 components issued during the most recent two years.

The strongest associations shown by this data collection and analyses were the association of failure to trace and test, and of death, with time since transfusion, age at transfusion and care under certain medical specialities.

Comparability with other lookback studies

The yield of HCV infections detected by published lookback programmes has varied along with other factors such as the criteria used to determine components to enter lookback, the procedures used to identify recipients, and the characteristics of the recipients that determine whether testing is performed.

The rates of tracing recipients, and identifying infections, are broadly similar - or within variations to be expected due to different methods - in other published lookbacks and our own. We report identifying 1 HCV infection for every 16 components entering lookback: 1 infection per 9, 10, and 21 components has been reported from Scotland[2], Northern Ireland[3] and Canada[4] respectively. We report identifying 1 HCV infection for every 8 recipients identified: 1 infection per 2, 4, 5, 5, 6, 8 and 22[5] recipients identified has been reported from Eire[8], Scotland, Northern Ireland, New Zealand[5],

Canada, Denmark[6] and The Netherlands [for PCR positive donors only][10] respectively. We report identifying 1 HCV infection for every 2 recipients tested: Eire, Northern Ireland, New Zealand and Canada also report 1 per 2 tests, and Scotland, Denmark and The Netherlands [for PCR positive donors] report 1 per 1 test. From these studies, the chance of being infected if tested as a lookback recipient appears to be consistent at approximately 50% for lookbacks on donations from anti-HCV positive donors, and approaching 100% in lookbacks on donations from HCV PCR positive donors. At the time of designing the lookback, PCR test results for donors were incomplete and were not considered a robust surrogate of infectivity at the time of previous donations. Had lookback been restricted to PCR positive donors, the reported data suggest only 10% of the components described would have entered lookback, and only 16% of the infected recipients identified by the this lookback would have been identified. However, under-reporting of donors' PCR test results to our dataset is likely. The yield of lookback at components from donors with a reported PCR positive test was 1 infected recipient for every 8 components entering lookback.

Mortality of transfusion recipients

Few contemporary data exist on the mortality of transfusion recipients. The recipients traced during this lookback provide a picture of mortality by age, sex, component type, speciality of transfusion and time since transfusion for recipients of blood transfusions prior to September 1991. Unfortunately, another variable expected to be strongly associated with mortality - the number and type of all transfusions given during the episode that including the HCV lookback component - was not recorded. Whether post-transfusion mortality has changed since the introduction of anti-HCV testing of blood donations in September 1991 is not known. Unfortunately, information about the cause of death was missing from our dataset for 54% of those known to have died by the time of tracing for HCV testing.

Factors affecting recipient testing

Year of transfusion and age at transfusion were independently associated with failure to test the recipients of transfused components.

Restricting lookback to components issued in the last 5 years (or 2 years), would (assuming no other changes in the lookback procedure's effectiveness) have resulted in 64% (or 33%) of the components described entered lookback, and 75% (or 45%) of the infected recipients identified by this lookback being identified.

Restricting follow-up to the 72% of recipients under 80 years old at the time of tracing (or 52% under 70, or 28% under 50) would have resulted in 93% (or 77% or 43%) of the infected recipients identified by the this lookback being identified.

Transfusion during care of a medical speciality with high mortality (oncology, care of the elderly and haematology with 84%, 71% and 69% found "known dead" respectively); was also associated with failure to test. The specialities with lowest mortality (obstetrics and gynaecology, paediatrics, cardiothoracic care and orthopaedics, with 13%, 28%, 40% and 31% found "known dead" respectively) had the highest yield of identified infected individuals for components transfused: 1 to 2.8, 1 to 3.6, 1 to 4.0 and 1 to 4.1 respectively. Together these four specialities accounted for 31% of the transfusions with speciality known (45% with recipient not known to be dead) , and 50% of the HCV infections detected.

The variables associated with being "not tested" in those not known to be dead, were similar to those associated with being "known dead", suggesting that death - although not recorded in the hospital notes - may have been the major reason for recipients falling into the "not tested" group.

Restriction of the components entered into lookback, and of the follow-up of identified recipients, could improve the efficiency of future lookbacks. Whether restrictions could be justified - at the cost of some un-identified infections - would depend on the expected natural history, probability of successful treatment, probability of secondary transmission of the infection, and on the opportunity cost of the process.

ACKNOWLEDGMENTS: We thank all the staff at blood centres, hospitals and laboratories who have been involved with the HCV lookback programme. Particular thanks go to the following individuals: Chris Bates, Peter Flanagan, Russell Hambleton, Sandra Hodgkins, David Howell, Virge James, Brian Johnston, Chris Jones, Avril Marshall, Cindy Mooring, Vijay Muddu, Alison Murray, Lucy Nolan, Kemmy Oyin-Adeniji, Peter Rogan, Jackie Serevitch, Alistair Shepherd, Khin Shwe, Dorothy Stainsby, Jennifer Whitehead, Susan Williamson.

TECHNICAL HELP: The authors thank Nick Andrews and Tom Nichols for advise and assistance with the statistical analyses in this paper.

* The English National Blood Service HCV Lookback Collation Collaborators: Dr N Anderson (NBS - Bristol), Dr C Chapman (NBS - Newcastle), Dr A Dike (NBS - Oxford), Dr G Gabra (NBS - Birmingham), Dr A Herborn (NBS - Southampton), Dr P Hewitt (NBS - North London), Dr C Llewelyn and Dr E Caffrey (NBS - East Anglia), Dr A Gorman (NBS - Brentwood), Dr N Hewson and Dr B Jones (NBS - Trent), Dr E Love (NBS - Manchester), Dr V Martlew (NBS - Mersey and North Wales), Dr A Townley (NBS - Leeds), Dr A Robinson (NBA), Ms K Soldan (NBA & Public Health Laboratory Service Communicable Disease Surveillance Centre), Dr H Harris and Dr Mary Ramsay (PHLS CDSC).

REFERENCES:

[1] The English National Blood Service HCV Lookback Collation Collaborators. Transfusion transmission of HCV infection prior to anti-HCV testing of blood donations in England: results of the national HCV lookback programme. *Transfusion* (***submitted January 2001***)

[2] Ayob Y, Davidson JI, Baxter A, Jordan A, Yap PL, Gillon J. Risk of hepatitis C in patients who received blood from donors subsequently shown to be carriers of hepatitis C virus. *Transfusion Medicine*, 1994;**4**:269-272.

[3] Morris K, Bharucha C. Completed hepatitis C lookback in Northern Ireland. *Transfusion Medicine*, 1997;**7**:269-275.

[4] Long A, Spurll G, Demers H, Goldman M. Targeted hepatitis C lookback: Quebec, Canada. *Transfusion*, 1999;**39**:194-200.

[5] Bullen C. Hepatitis C lookback programme highlights the value of blood donor screening. *The New Zealand Public Health Report*, 1997;**4**:73-75.

[6] Christensen PB, Groenboek K, Krarup HB, and the Danish HCV Lookback Group. Transfusion acquired hepatitis C: the Danish lookback experience. *Transfusion* 1999;**39**:188-193.