Estimation of the Number of Individuals Infected and Alive in 2011 as a Consequence of Blood Transfusion in Scotland 1970 — 1991.

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1. Introduction

The following is Health Protection Scotland's response to a request from the Penrose Enquiry. The analysis, undertaken by HPS (Professor David Goldberg and Dr Christian Schnier), was informed by advice from Drs Jack Gillon and Brian McClelland who are contributing to the Penrose Enquiry in an SNBTS capacity.

2. Aim

1. To estimate the number of people who acquired HCV infection as a consequence of blood transfusion in Scotland during 1970 - 1991.
2. To estimate the number of people alive and infected in 2011 who acquired infection HCV as a consequence of blood transfusion in Scotland during 1970 - 1991.

3. Definitions, Assumptions & Model

3.1. Definitions

Unit. The term 'blood component units' (shortened to 'units') is used here to denote any labile component of a whole blood donation, ie red cells, platelets, plasma or cryo-precipitate. All units from RNA-positive donors (denoted as 'HCV-contaminated unit') are assumed to be equally infectious when transfused to a recipient (Assumption i).

HCV infection. The term 'HCV infection' here is used to denote a state in which viral replication is taking place in a patient. All recipients of HCV-contaminated units are assumed to develop HCV infection (Assumption i). Approximately 25% of patients with HCV infection are assumed to clear the infection within 6 months of acquisition (Assumption ii). Patients who have cleared the infection will test RNA negative but antibody positive; they are assumed to be non-infectious.

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3.2. Assumptions

Assumption i *Proportion of recipients of HCV contaminated units that develop HCV infection.* We assumed that every recipient of a contaminated unit (independent of the type of unit) subsequently developed HCV infection. It is theoretically possible that a unit obtained from an infectious donor might not be infectious as a consequence of viral inactivation incurred during the donation/storage process.

Assumption ii *Proportion of HCV antibody positive donors who are RNA positive (infectious).* It was assumed that 75% of HCV-antibody positive donors were RNA (virus) positive and therefore infectious (The Global Burden of Hepatitis C Working Group, 2004).

Assumption iii *Reduction in the number of HCV-positive donors in the donor population as a result of deferral policy.* Deferral policy, introduced by SNBTS in 1984, was assumed to have reduced the HCV prevalence in the donor population constantly by 66%. This assumption was based on limited local data and expert opinion.

Assumption iv *HCV prevalence in the donor population between 1970 and 1990.* The first available observed data on the prevalence of HCV antibodies among the Scottish blood donor population applies to September 1991 to February 1992. The HCV prevalence in the donor population for each year between 1970 and 1990 was assumed to be proportional to the estimated number of HCV infected injecting drug users (IDU) alive during each year of the period, as above (Hutchinson, 2005). The rationale of assuming proportionality is that it is estimated that 90% of HCV-infected individuals in Scotland acquired their infection directly through injecting drug use and that an appreciable proportion of the remainder will have acquired infection indirectly as a consequence of injecting drug use (e.g., being born to an infected IDU or having unprotected sex with an infected IDU)(Hutchinson et al., 2006).

Assumption v *Number of units generated from one blood donation.* Each unit of donated blood was assumed to have been split into 1.25 units. This assumption was based on limited local data and expert opinion.

Assumption vi *Proportion of units transfused.* Approximately 56% of the donated blood was assumed to have been transfused, with all units having the same probability of being transfused. Assumptions were based on limited local data and expert opinion.

Assumption vii *Number of recipients expected to receive more than one HCV contaminated unit.* The risk of receiving two or more contaminated units is approximately 0.0007% – a risk which is negligible. Accordingly, it was assumed that all HCV-contaminated units were transfused to different patients.

Assumption viii *Age at transfusion of a contaminated unit.* The age distribution of people receiving a blood transfusion was assumed not to have changed drastically between the years 2010/2011 (for which data were available,(Table 10 in the Appendix)) and 1970. This assumption was based on limited local data and expert opinion.

Assumption ix *Effect of HCV-infection on* post *transfusion survival rate.* We assumed that the survival rate of recipients of HCV contaminated units did not differ from the survival rate of recipients of non-contaminated units. This assumption was based on Harris et al. (2006), who showed that for the first 16 years *post* transfusion, all-cause mortality in 924 HCV-infected transfusion recipients (cases) and 475 anti-HCV negative transfusion recipients (controls) did not differ significantly. Information about later survival of that cohort was not available.

Assumption x *Survival rate* post *transfusion to 2011.* Age-stratified 5-year survival after transfusion was assumed to be similar to 5-year survival in North England (Wallis, 2004). Survival after those 5 first years *post* transfusion to 2011 was assumed to be similar to the survival of the general population in Scotland and that life expectancy for the period between 1970 and 2011 did not change enough to significantly influence survival in the context of the size and the age, at transfusion, of the infected cohort; life expectancy data for 2000-2002 were used in the model.

3.3. Model

We first developed a deterministic model based on available data, literature and expert opinion and then transformed it into a stochastic, probabilistic simulation model. This was undertaken to express uncertainty in the assumptions; for example, we replaced the estimate of the number of units generated from one blood donation in the deterministic model (1.25 ; Assumption v) with a range of possible values in the simulation model (quite likely between 1.125 and 1.6, with the most likely value of 1.25). Model parameters (e.g., most likely values and distributions) that were used in @Risk are listed in table 11 in the Appendix. The modeling environment was Excel, with the @Risk (Palisade, Newfield, NY) risk-analysis and simulation add-in for Excel. Simulations were run with 10,000 iterations. Because of the nature of the distributions in the assumptions, results from the deterministic model and the stochastic model are expected to differ slightly.

4. Number of people who acquired HCV as a consequence of blood transfusion in Scotland during 1970 - 1991

Estimates were based on (a) HCV prevalence in the donor population and (b) number of units transfused between 1970 and 1991.

4.1. Methods

4.1.1. HCV prevalence in the donor population

HCV prevalence in donors who donated during September 1991 to February 1992.. In September 1991 to February 1992, 159 of 180,000 donors tested HCV-antibody positive

Table 1: Estimated prevalence of HCV-positive infectious donors in Scotland before (1970-1983) and after (1984-1991) the introduction of donor deferral.

Year	Prevalence[%]
1970	0.006
1971	0.007
1972	0.008
1973	0.009
1974	0.009
1975	0.010
1976	0.011
1977	0.015
1978	0.019
1979	0.024
1980	0.030
1981	0.038
1982	0.051
1983	0.067
1984	0.029
1985	0.037
1986	0.045
1987	0.050
1988	0.054
1989	0.059
1990	0.063
1991	0.066

(0.088%). Of those 159 donors 25% were assumed to be RNA-negative (i.e., not infectious)(Assumption ii); therefore the prevalence of HCV-positive infectious donors in the donor population in 1991 was estimated to be 0.066% (95% CI: 0.055% to 0.079%).

HCV prevalence in donors before 1991. To estimate the prevalence of HCV-positive infectious donors in the population before 1991, we assumed (Assumption iv) that the change in the estimated number of HCV-infected IDU between 1970 and 1991 (Table 8 in the Appendix) was proportional to the change in HCV-prevalence among the donor population (for example, the estimated number of HCV-infected IDU in 1985 was approximately 56% of the estimated number of HCV-infected IDU in 1991. Therefore, the estimated HCV prevalence in the donor population in 1985 was predicted to be 56% of the estimated prevalence in the donor population in 1991.)

In 1984, SNBTS introduced a deferral policy to reduce the number of donors with a higher risk of having blood born virus infections; therefore the prevalence of HCV-positive infected donors in the donor population during 1984 to 1991 was lower than it would have been, if the deferral policy had not been in operation. It was assumed that the deferral policy reduced HCV-prevalence in the donor population by 66% (Assumption iii).

Table 1 shows the estimated prevalence in the donor population by year of donation.

Table 2: Number of donations before the introduction of HCV testing and the estimated number of units transfused, Scotland 1970-1991.

Year	Observed No donations	Estimated No units transfused
1970	244463[a]	171124
1971	248216[a]	173751
1972	252026[a]	176418
1973	255895[a]	179127
1974	259823[a]	181876
1975	248558	173991
1976	262549	183784
1977	277772	194440
1978	283306	198314
1979	290078	203055
1980	289324	202527
1981	293501	205451
1982	297851	208496
1983	302233	211563
1984	308617	216032
1985	304914	213440
1986	309748	216824
1987	289006	202304
1988	310785	217550
1989	321588	225112
1990	331979	232385
1991[b]	238906	167234

[a]Estimated (see 4.1.2)
[b]January-August

4.1.2. Number of units transfused between 1970 and 1991

Number of donations. Table 2 shows the number of blood donations between 1970 and 1991 that were donated before HCV antibody testing commenced. The figures for 1970 to 1974 were not available from file but were predicted using a Poisson regression model from the other years. Because HCV antibody testing of blood donors was introduced in Sept. 1991, the figure for 1991 was 66% of the total annual number for 1991.

Number of units. After donation, each donation is split into units. To estimate the number of units donated, the number of donations was multiplied by 1.25 – the number of units per donation (Assumption v).

Number of units transferred. Only a proportion of units donated are transfused. To estimate the number of units that were transfused, the number of units donated was multiplied by 56% – the proportion of units assumed to have been transfused (Assumption vi).

Table 3: Simulation results: Number of people who acquired HCV as a consequence of blood transfusion in Scotland during 1970 - 1991.

Year	Estimated no of recipients of HCV-contaminated units		
	5%	Median	95%
1970	5	11	18
1971	6	12	21
1972	7	14	24
1973	8	16	26
1974	9	18	29
1975	10	19	30
1976	12	22	34
1977	18	30	46
1978	24	39	58
1979	33	51	74
1980	42	63	91
1981	55	82	116
1982	76	111	156
1983	103	148	205
1984	46	66	89
1985	61	83	111
1986	75	102	134
1987	78	106	139
1988	93	124	163
1989	106	141	184
1990	117	155	202
1991[a]	87	116	154
Total[b]	1198	1533	1963

[a]January-August

[b]Total statistics are results from simulations and do not equate to the sum of the simulation results by year between 1970 and 1991.

4.1.3. Estimating the number of recipients infected

For each year, the number of people exposed to contaminated blood products was calculated by multiplying the estimated prevalence in the donor population by the estimated number of units transfused.

4.2. Results: Number of people exposed to contaminated blood products between 1970 and 1991

It is estimated that during 1970 – 1991 (to August) 1533 (90% Credibility interval: 1198 to 1963) contaminated units were transfused (Table 3). Because it was assumed that every transfused contaminated unit resulted in HCV infection (Assumption i) and that no recipient received more than one contaminated unit (Assumption vii), it is estimated that, in total, 1533 (1198 to 1963) recipients were infected.

5. Survival until 2011

Estimates of the number of infected people alive in 2011 were based on (a) year 5 *post* transfusion survival and (b) long-term survival after year 5 *post* transfusion. The reason for this is that blood transfusion is a determinant of survival in the first 5 years *post* transfusion but not thereafter. Note, the evidence indicates that HCV infection *per se* would not have influenced survival during the first 16 years *post* acquisition of infection following transmission; though it is known that HCV infection influences survival in the longer term, the effect in this transfusion infected cohort is likely to have been very small (and thus not statistically discernable) in the context of (i) the small number of, generally, older people who are/were vulnerable to so many other conditions and (ii) the fact that Hepatitis C infection only results in life threatening disease in a minority of those infected; accordingly, no effect of HCV on survival was included in the model (Assumption ix).

5.1. Methods

5.1.1. Year 5 post *transfusion survival*

Age at transfusion. For the 1533 individuals estimated to have been infected with contaminated units, age at transfusion was estimated using an age distribution of recipients of blood units from 2010/2011 (Table 10 in the Appendix; Assumption viii). Table 4 shows estimated age of recipients at blood transfusion.

Year 5 post *transfusion survival by age at transfusion.* Year 5 survival probabilities stratified by age at transfusion were informed by Wallis (2004) (Table 9 in the Appendix). Table 5 shows the estimated number of HCV infected people in each age group by year of transfusion likely to have survived the first 5 years *post* transfusion.

5.2. Survival from year 5 post *transfusion to 2011*

Survival after year 5 *post* transfusion was assumed to be similar to survival in the general population in 2000-2002 (Assumption x) and was therefore calculated using actuarial tables from General Register Office for Scotland (2006).

For recipients, for example, who were 10-20 year old at blood transfusion, survival was calculated for 20 year old recipients (midpoint 15 (of 10-20 year age band) plus 5 years follow up *post* transfusion). The survival period was the period from year 5 *post* transfusion to 2011 (26 years for a recipient in 1980). Thus, for recipients who were 10-20 year old at blood transfusion in 1980, we calculated the 26 year survival probability of a 20 year old person. For recipients in other age group, survival probabilities were calculated accordingly.

Table 4: Estimated no of infected recipients by age of transfusion and transfusion year (numbers based on deterministic model).

Year	No infected	Age group at transfusion									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
1970	10	0	0	0	1	1	1	2	3	2	0
1971	12	0	0	0	1	1	2	3	3	2	0
1972	14	0	0	0	1	1	2	3	4	2	0
1973	16	0	0	1	1	1	2	3	4	3	1
1974	18	1	0	1	1	1	2	4	4	3	1
1975	18	1	0	1	1	1	2	4	5	3	1
1976	21	1	0	1	1	2	3	4	5	4	1
1977	30	1	1	1	1	2	4	6	8	5	1
1978	38	1	1	1	2	3	5	8	10	7	1
1979	50	2	1	2	3	4	6	10	13	9	2
1980	62	2	1	2	3	5	8	13	16	11	2
1981	80	2	2	3	4	6	10	16	20	14	3
1982	108	3	2	4	5	8	13	22	27	19	3
1983	144	4	3	5	7	11	18	29	36	25	5
1984	64	2	1	2	3	5	8	13	16	11	2
1985	81	2	2	3	4	6	10	17	20	14	3
1986	99	3	2	4	5	8	12	20	25	17	3
1987	102	3	2	4	5	8	13	21	26	18	3
1988	121	4	2	4	6	9	15	25	31	21	4
1989	137	4	3	5	7	11	17	28	35	24	4
1990	150	5	3	5	8	12	18	31	38	26	5
1991[a]	113	3	2	4	6	9	14	23	29	20	4

[a]January-August

Table 5: Estimated no of infected recipients who survive the first 5 years *post* transfusion by age of transfusion and transfusion year (numbers based on deterministic model).

Year	No infected	Age group at transfusion									
		0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79	80-89	90-99
1970	10	0	0	0	0	0	1	1	1	0	0
1971	12	0	0	0	0	1	1	1	1	0	0
1972	14	0	0	0	1	1	1	1	1	1	0
1973	16	0	0	1	1	1	1	2	1	1	0
1974	18	0	0	1	1	1	1	2	2	1	0
1975	18	0	0	1	1	1	1	2	2	1	0
1976	21	1	0	1	1	1	1	2	2	1	0
1977	30	1	0	1	1	1	2	3	3	1	0
1978	38	1	1	1	2	2	2	4	3	1	0
1979	50	1	1	2	2	2	3	5	5	2	0
1980	62	2	1	2	2	3	4	6	6	2	0
1981	80	2	1	3	3	4	5	8	7	3	0
1982	108	3	2	4	4	5	7	11	10	4	0
1983	144	4	2	5	6	7	9	14	13	5	1
1984	64	2	1	2	3	3	4	6	6	2	0
1985	81	2	1	3	3	4	5	8	7	3	0
1986	99	2	2	3	4	5	6	10	9	4	0
1987	102	3	2	3	4	5	6	10	9	4	0
1988	121	3	2	4	5	6	7	12	11	4	0
1989	137	3	2	5	5	6	8	13	12	5	0
1990	150	4	2	5	6	7	9	15	14	5	1
1991[a]	113	3	2	4	5	5	7	11	10	4	0

[a]January-August

Table 6: Simulation results: Estimated number of antibody positive recipients alive in 2011 by year of transfusion.

Year	No of recipients alive		
	5%	Median	95%
1970	0	1	3
1971	0	1	4
1972	0	1	4
1973	0	2	5
1974	0	2	5
1975	0	2	6
1976	0	3	6
1977	1	4	9
1978	2	6	11
1979	3	8	14
1980	5	10	17
1981	7	13	22
1982	11	19	30
1983	16	26	39
1984	6	12	19
1985	9	16	24
1986	12	20	30
1987	14	22	32
1988	17	27	39
1989	21	32	45
1990	25	36	51
1991[a]	18	29	41
Total[b]	228	296	384

[a]January-August

[b]Total statistics are results from simulations and do not equate to the sum of the simulation results by year between 1970 and 1991.

5.3. Result: Number of infected recipients of contaminated blood alive in 2011

We estimate that in total 296 (228 to 384) HCV infected recipients of contaminated blood were alive in 2011 (Table 6). Using the deterministic model, the youngest survivor was estimated to be 35 years old in 2011, the oldest 97 years. Mean age in 2011 was 61 years.

5.4. Result: Number of infected recipients of contaminated blood alive and RNA positive in 2011

Off the total 296 HCV infected recipients of contaminated blood still alive in 2011, it is estimated that 222 (166 to 294) (75%, Assumption ii) were still RNA positive and at increased risk of progressing to liver cirrhosis (Table 7). This estimate does not account for an uncertain number of individuals who have cleared the virus as a consequence of antiviral therapy.

Table 7: Simulation results: Estimated number of recipients alive and infected in 2011 by year of transfusion.

Year	No of recipients alive and infected		
	5%	Median	95%
1970	0	1	3
1971	0	1	3
1972	0	1	3
1973	0	1	4
1974	0	2	4
1975	0	2	5
1976	0	2	5
1977	1	3	7
1978	1	4	8
1979	2	6	11
1980	3	7	13
1981	5	10	17
1982	7	14	23
1983	11	20	31
1984	4	9	15
1985	6	12	19
1986	8	15	24
1987	9	16	25
1988	12	20	30
1989	15	24	36
1990	17	27	40
1991[a]	13	21	32
Total[b]	166	222	294

[a]January-August

[b]Total statistics are results from simulations and do not equate to the sum of the simulation results by year between 1970 and 1991.

6. Literature

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7. Appendix

Table 8: Estimated number of infected IDUs, Scotland 1970-1991 (Hutchinson, 2005) .

Year	No HCV infected IDUs
1970	575
1971	668
1972	740
1973	829
1974	910
1975	996
1976	1096
1977	1436
1978	1812
1979	2306
1980	2857
1981	3654
1982	4876
1983	6401
1984	8316
1985	10689
1986	12882
1987	14279
1988	15676
1989	17136
1990	18244
1991	19097

Table 9: 5-year survival probabilities in North England (Wallis, 2004) .

Age group	p(survival)
0	0.78
1-9	0.85
10-19	0.78
20-29	0.94
30-39	0.79
40-49	0.61
50-59	0.5
60-69	0.48
70-79	0.36
80-89	0.21
90-99	0.11
100+	

Table 10: Age distribution of recipients of units (Scotland, Financial year 2010/11.)

Agegroup	Sex	No units	Sex	No units	Proportion
0-9	Female	2760	Male	2867	0.030
10-19	Female	1564	Male	2246	0.020
20-29	Female	4046	Male	2640	0.036
30-39	Female	5608	Male	3794	0.050
40-49	Female	6754	Male	7668	0.077
50-59	Female	10607	Male	12370	0.123
60-69	Female	16294	Male	21837	0.204
70-79	Female	21586	Male	25673	0.253
80-89	Female	16748	Male	15587	0.173
90-99	Female	3865	Male	2133	0.032
100+	Female	92	Male	36	0.001
unknown	Female	39	Male	38	0.000

Table 11: Parameters used in @Risk

HCV Prevalence in 1991	RiskBeta(159,180000) [a]
RNA positivity	RiskPert(0.675,0.75,0.825) [b]
No units per donation	RiskPert(1.125,1.25,1.6)
Proportion used	RiskPert(0.5, 0.56, 0.66)
Deferral	RiskPert(2,3,4)
No antibody positive donations	RiskBinomial(No of donations, Antibody positive prevalence in donor population)[c]
No RNA positive donations	RiskBinomial(No antibody positive donations, RNA positivity)
No RNA positive units	RiskBinomial(No RNA positive donations, No units per donation)
No RNA positive units used	RiskBinomial(No RNA positive units, Proportion used)
Proportion of transfusions in age group($_i$)	RiskBeta(Number of transfusions in 2010/11 in age group($_i$), Number of transfusions in 2010/11 in other age groups)
No RNA positive units used in age group($_i$)	RiskBinomial(No RNA positive units used,Proportion of transfusions in age group($_i$))
5-year survival after blood transfusion in age group($_i$)	RiskBeta(No individuals in age group($_i$) who have survived, No individuals in age group($_i$) who have not survived) (Wallis, 2004)
No infected recipients in age group($_i$) who survive first 5 years after transfusion	RiskBinomial(No RNA positive units used in age group($_i$),5-year survival after blood transfusion in age group($_i$))
No infected recipients in age group($_i$) who survive from 5 years *post* transfusion to 2011	RiskBinomial(No infected recipients in age group($_i$) who survive first 5 years after transfusion,survival risk in Scottish Population)

[a] RiskBeta(alpha1,alpha2) specifies a beta distribution using the shape parameters alpha1 and alpha2. These two arguments generate a beta distribution with a minimum value of 0 and a maximum value of 1.

[b] RiskPert(minimum, most likely, maximum) specifies a PERT distribution (as special form of the beta distribution) with a minimum and maximum value as specified. The shape parameter is calculated from the defined most likely value.

[c] RiskBinomial(n, p) specifies a binomial distribution with n number of trials and p probability of success on each trial. The number of trials is often referred to as the number of draws or samples made.