Title: **The contribution of transfusion to HCV infection in England**

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The contribution of transfusion to HCV infection in England

Abstract

Objectives: To estimate the total number of individuals infected with HCV by blood transfusion in England, and the number expected to be alive.

Design: A model of the path from the collection of donations from HCV infected donors to the infection of recipients was constructed using data collected during the English HCV lookback programme. Components that fell out of the lookback programme at various stages prior to recipient testing, and components from HCV infected donations that never entered lookback, were entered into the model to produce an estimate of the number of resulting recipient infections (dead and alive at the end of 1995).

Main outcome measures: Numbers of transfusion transmitted HCV infections.

Results: Less than 14,000 blood recipients were estimated to have been infected with HCV during the decade prior to the start of donation testing. Over 60% of these were expected to have died by the end of 1995. 677 (5%of total, 13% of living) of these infections were identified by the HCV lookback.

Conclusions: Transfusion, prior to the testing of blood donations for anti-HCV, infected a large group of individuals. However, this group constitutes a very small, and declining, proportion of all HCV infections in the population.

(199 words)

What this paper adds:

What is already known on this subject?

Transfusion prior to anti-HCV testing of blood donations has resulted in many HCV infections. Some of these infections have been diagnosed by testing as a result of the HCV lookback programme.

What does this study add?

In England, approximately 14,000 individuals may have been infected by transfusion. The majority of these infections were not identified by the HCV lookback programme. However, transfusion is only responsible for a very minor proportion of HCV prevalence in the population of England.

This week in the BMJ

Transfusion transmitted HCV

Approximately 3-7% of HCV infections in England may have been acquired by blood transfusion. A major programme of tracing and testing (lookback) the recipients of blood donations collected before donation testing for anti-HCV has been conducted. This lookback has identified some transfusion transmitted HCV infections, and has provided other data that have been used to estimate that around 14,000 HCV infections were transmitted by transfusion prior to the introduction of donation testing for anti-HCV. More than 60% of these are expected to have already died from other causes. Investigation into the extent of HCV-related disease in these recipients is ongoing.

(103 words)

Introduction

The HCV lookback programme in England has attempted to trace patients transfused prior to September 1991 with blood from donors who were found to be positive for hepatitis C antibodies (anti-HCV) after routine testing for anti-HCV was introduced in September 1991. The aim of this lookback was to diagnose patients with transfusion transmitted HCV who might benefit from care and treatment. For various reasons including loss of records, movement of patients, death of patients and attention to patients' best interests and wishes, not all components entering lookback resulted in recipients receiving testing. Also, as not all HCV infected donors gave blood after anti-HCV testing was introduced, many infected donations collected prior September 1991 will not have been subsequently identified and will not have entered the lookback. We have used data collected during the lookback to construct a model of the path from donation to recipient infection in order to estimate the total number of transfusion transmitted HCV infections, and therefore derive the contribution of transfusion to HCV infection in England.

Methods

Data from all stages of the lookback process - about infected donors, blood components (red cells, platelets, FFP and cryoprecipitate) made from donations by these donors, components transfused, identified recipients, tested recipients, and infected recipients - were collected from eight blood centres that handled 80% of all blood components entering the lookback in England. Information about all HCV tested recipients was collected from all centres[1].

These data were used to construct a model of the path followed by a lookback component, with the observed proportion following each branch taken to predict the probability that non-observed components would follow the same route.

The number of HCV infections transmitted by components that entered lookback but did not complete the lookback path to a tested recipient was estimated by assuming

that they would have followed the same path as those that completed lookback i.e. by re-entering them into the model at the point at which they fell out of the lookback process.

The number of donations collected between 01/01/1980 and 01/09/1991, and the number of anti-HCV positive donations collected during the first four months of anti-HCV testing was obtained from donation testing records. The total number of anti-HCV positive donations collected during the 1980s and until September 1991 was estimated by assuming that the prevalence of anti-HCV observed during the first four months of donor testing (0.066%) existed throughout this time. The number of anti-HCV positive components from donors who were not subsequently tested for anti-HCV (and therefore did not entered into the lookback) was then derived by subtraction of the number of components that did enter lookback. These extra (non-lookback) HCV infected components were then entered into the top of the model to, again, estimate the number of infections they are expected to have caused, and the number of those infected recipients expected to have died by the end of 1995.

Results

The observed outcomes at each stage of the lookback process on route to HCV testing for the 80% of components from the eight centres providing full datasets are shown in Table 1. Six-hundred and sixty-nine HCV infected recipients were identified from the 1,062 tested recipients from the eight centres in Table 1 plus 271 tested recipients receiving other lookback components. The infection rate in tested recipients (excluding 124 tested recipients with insufficient test results to determine HCV status) was 55%. 10% of the identified infections had been diagnosed prior to the lookback. Figure 1 shows the resulting model of the path from donation to infected recipient. This model estimated the number of transfusion transmitted HCV infections from components that entered lookback but fell out of the process prior to recipient testing to be 3,373 HCV infections (946 with fate of component not traced, 107 known to

have been transfused but with no recipient identified, 1870 known to have been transfused and to have died by end of 1995, and 450 who declined testing). Of these infections, 55% (1870) were known to be dead and an additional 19% (645) were expected to have died by the end of 1995.

25,864,035 donations were collected over the period 01/01/1980 to 01/09/1991, including an estimated 17,086 anti-HCV positive donations. If - as observed for the lookback donations - each donation resulted in 1.6 components, there were 26,647 components issued from anti-HCV positive donors. How many of these components were identified to enter the lookback is uncertain. 9,756 of the lookback components were collected between 1st January 1980 and the start of anti-HCV testing. If we assume that all these lookback components were anti-HCV positive, then they constitute 37% of the estimated total number of anti-HCV positive components issued during this time period, and 16,891 (63%) anti-HCV positive components did not enter the lookback. Entry of these extra anti-HCV positive components into the model predicts an extra 10,905 transfused recipients, and an extra 6,034 HCV infected recipients of which 3,681 are expected to have died by the end of 1995. However, it is unlikely that all the components that were identified for lookback (by subsequent anti-HCV positivity of their donor) were anti-HCV positive. Approximately 75% of anti-HCV positive donors have been found to be HCV RNA positive by PCR. If we assume that only RNA positive donations transmit HCV infection, we would expect 75% of anti-HCV positive components to transmit. If so, our observation that only 55% of lookback components result in HCV infection can be used to estimate that 73% of lookback components were anti-HCV positive. (The remaining 27% of lookback donations where presumably collected while the donor was anti-HCV (and HCV RNA) negative.) If only 73% of lookback components were anti-HCV positive, then an extra 19,525 (73% of 26,647) anti-HCV positive components did not enter the lookback. Entry of these extra anti-HCV positive components into the model - with the use of a 0.75 probability of infection transmission for these components - predicts an

extra 12,606 transfused recipients, and an extra 9,454 HCV infected recipients of which 5,794 are expected to have died by the end of 1995.

In total, we therefore estimate that there have been 13,504 HCV infections transmitted by transfusion from lookback components, and other HCV infected blood components issued in the 1980s. 8,317 of these are known or expected to have died by the end of 1995.

Figure 2 shows the total observed and estimated numbers of transfusion transmitted infections.

Table 1: Summary of the outcome for 80% (9,222) of blood components entering lookback in England

	Number	*%*	*Number dropping out prior to recipient testing*
• Components transfused (2,517 discarded/other uses)	4,586	65% of traced components	2,119 untraced fate
• Recipients identified (including 8 x 2 components)	4,424	96% of components transfused	154 recipients not identified
• Recipients not known dead	1,713	39% of components transfused	2,711 known dead
• Recipients tested	1,062	62% of those not known dead	651 not tested

Figure 1: Model of the path from donation to infected recipient and other outcomes.

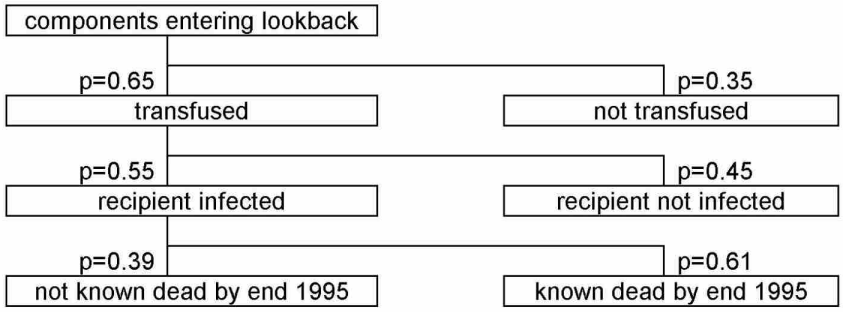
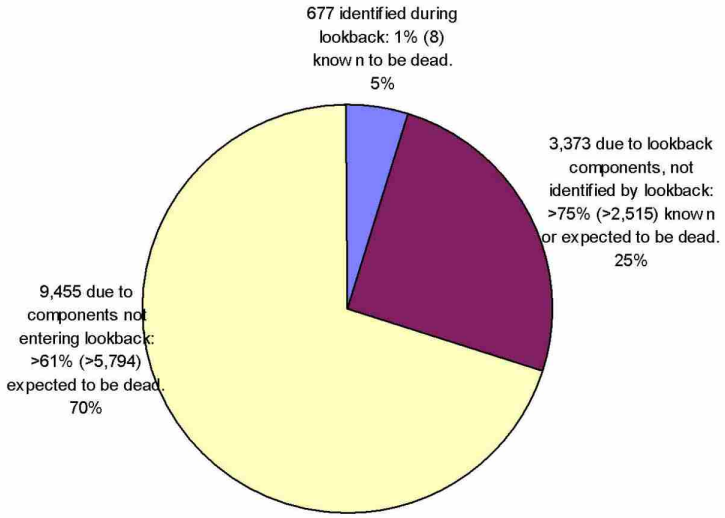


Figure 2: Estimated total transfusion transmitted HCV infections, England 01/01/1980-01/09/1991



Discussion

These data, and the model used, give an indication of the likely number of transfusion transmitted infections, and of the contribution transfusion has made to HCV infection in England. There were - by necessity - many assumptions and extrapolations used in our model, and the results are not therefore expected to be exact.

We estimate that the HCV lookback has identified about 5% (677) of the total number of HCV infections transmitted by transfusion since 01/01/1980, and over 13% of infected recipients who survived to 1995. It has been estimated that there are between 200,000 and 400,000 infected individuals living in the UK[2]: if this is so, transfusion appears to account for between 3% and 7% of all infections.

Laboratory reports of HCV infection - which are biased towards those individuals who are offered testing - are in accord with these estimates. Transfusion was reported as the most probable route of infection for 4.3% (128) of laboratory reports of HCV infection with risk factor information in England and Wales during 1992-1996[3].

Of the infections identified by the lookback, 10% had already been diagnosed. The proportion of infections not identified by the lookback that have already been diagnosed may be lower if individuals not identified by the lookback are less likely to be in contact with health services, or higher if individuals not tested during the lookback were more likely to be known anti-HCV positives.

Other analyses of data from the lookback[1] imply that our estimates of the proportions of unidentified infections that have died based on frequency of “known dead” recipients will be conservative. When calculated by year, the majority of the “extra” components (from donors not did not donate after September 1991) not included in the lookback were collected and transfused longer ago - during the first half of the 1980s. Also, there will be some (approximately 1%) multiply transfused recipients who received more than one of these “infections”. Our model’s estimate of living transfusion transmitted infections (in 1995) is therefore a maximum estimate.

We may have underestimated or overestimated the infections transmitted in the 1980s by using the prevalence of infection at the start of testing without accounting for selective removal of infected donors during the 1980s, or accumulation of prevalence over time. This uncertainty, and others, prohibit including earlier years. If recipients infected during the 1970s and 1960s were similar to the identified lookback recipients (transfused during 1980s), their average age at the start of 1995 would be 74 and 84 years respectively.

Only 2 transfusion transmitted HCV infections have been reported from anti-HCV tested components during the past six years[4] (up to end 2000), and the risk of infection by transfusion is being reduced further by nucleic acid testing. Transfusion transmission of HCV in UK is therefore largely a thing of the past, although the extent of continuing secondary transmission has not been established, and investigation of the burden of disease amongst infected recipients is ongoing[5].

word count = 1,550

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Contributors: All the collaborators participated in the data collection for this paper and contributed to the interpretation of the data analyses. Kate Soldan analysed the data and is the guarantor. KS and Mary Ramsay prepared the paper.

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