The contribution of transfusion to HCV infection in England

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SUMMARY

The English HCV lookback programme has identified some individuals with transfusion-transmitted HCV infection. The path from the collection of donations from HCV-infected donors to the identification of infected recipients was constructed. The probability of different outcomes at each branch was derived from data collected during this programme. This path of probabilities was then used to produce a complete estimate of the number of recipients infected by blood transfusions (dead and alive at the end of 1995) by re-entry of blood components that fell out of the lookback at various steps prior to recipient testing, and entry of components from HCV-infected donations that were never identified for lookback. Less than 14 000 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. Transfusion has infected a large group of individuals. However, this group constitutes a very small, and declining, proportion of all HCV infections in the population.

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 virus antibody (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

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records, movement of patients, death of patients and attention to patients' best interests and wishes, not all recipients of blood from known anti-HCV-positive donors received testing. Also, as not all HCV-infected donors gave blood after anti-HCV testing was introduced, many infected donations collected between 1 January 1980 and September 1991 will not have been subsequently identified and will not have entered the lookback programme. We have used data collected during the lookback programme to derive the probabilities of infected donations resulting in infected recipients, and then to estimate the total number of transfusion-transmitted HCV infections, and therefore 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 programme in England. Information about all HCV-tested recipients was collected from all centres [1].

These data were used to construct the path followed by a lookback component, with the observed proportion following each branch taken to predict the probability that components with an unidentified fate would follow the same route. For components that entered the lookback programme but did not reach the end of the path (i.e. recipient testing), the numbers observed in our 80% sample were multiplied by 1·25 (i.e. 100/80) to estimate the total numbers. The number of HCV infections transmitted by these components that were included in the lookback programme but did not complete the lookback path to a tested recipient was then estimated by assuming that they would have followed the same path as those that completed the lookback, i.e. by re-entering them onto the path to testing at the point at which they fell out of the lookback process.

The number of donations collected between 1 January 1980 and 1 September 1991, and the number of confirmed anti-HCV-positive donations collected during the first 4 months of anti-HCV testing were 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 4 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 not entered into the lookback programme) was then derived by subtraction of the number of components that did enter the lookback programme. These extra (non-lookback) HCV-infected components were then entered into the top of the path from component release to recipient test result to 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 en route to HCV testing for the 80% of components from the eight centres providing full datasets are shown in the middle column of Figure 1. A total of 677 HCV-infected recipients were identified from the 1062 tested in the eight centres that provided full information about each component and the 271 tested recipients who received other components from anti-HCV-positive donors identified in the lookback programme. 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 programme. The median age of these infected individuals in 1995 was 55 years.

The observed probabilities of the outcome of interest at each stage on the lookback path are also shown in Figure 1; these formed the path from donation to infected recipient that was then assumed to also have applied to components that did not complete the stages on this path. This estimated the number of transfusion-transmitted HCV infections from components that entered the lookback programme but fell out of the process prior to recipient testing to be 3373 HCV infections. This included 946 infections acquired from components with their fate not traced (i.e. without rounding errors; $2649 \times 0.65 \times 0.55$), 107 infections from components known to have been transfused but with no recipient identified (i.e. 193×0.55), 1870 infections from components transfused to recipients who were known to have died by the end of 1995 (i.e. 3389×0.55), and 450 infections

Expected anti-HCV positive components (01/80–08/91) not entering the lookback programme

Observed path of components that entered the lookback programme and resulted in known HCV status of recipients

Components that entered the lookback programme but their fate, or the HCV status of their recipients is unknown

19525 anti-HCV positive components not entering the lookback programme

80% (9222) of components entering the lookback programme

2119 components with fate not traced *(2649 after adjustment to 100%)*

65% (4586/7103) transfused

(39% 1713/4424 of identified recipients assumed alive

154 components with no recipient identified *(193 after adjustment to 100%)*

2711 recipients known dead *(3389 after adjustment to 100%)* (8 known infected)

1062/1713 (62%) of assumed alive recipients tested

651 recipients not tested *(814 after adjustment to 100%)*

Plus 271 tested recipients of the other 20% of components entering the lookback programme

677/1209 (55%) tested recipients HCV infected

124 with insufficient test results

Assuming follow same path as observed components

Assuming follow same path as observed components

9455 infections due to components, not entering lookback: >61% (>5794) expected to be dead.

677 infections identified during lookback: 1% (8) known to be dead.

3373 infections due to lookback components, not identified by lookback: >75% (>2515) known or expected to be dead.
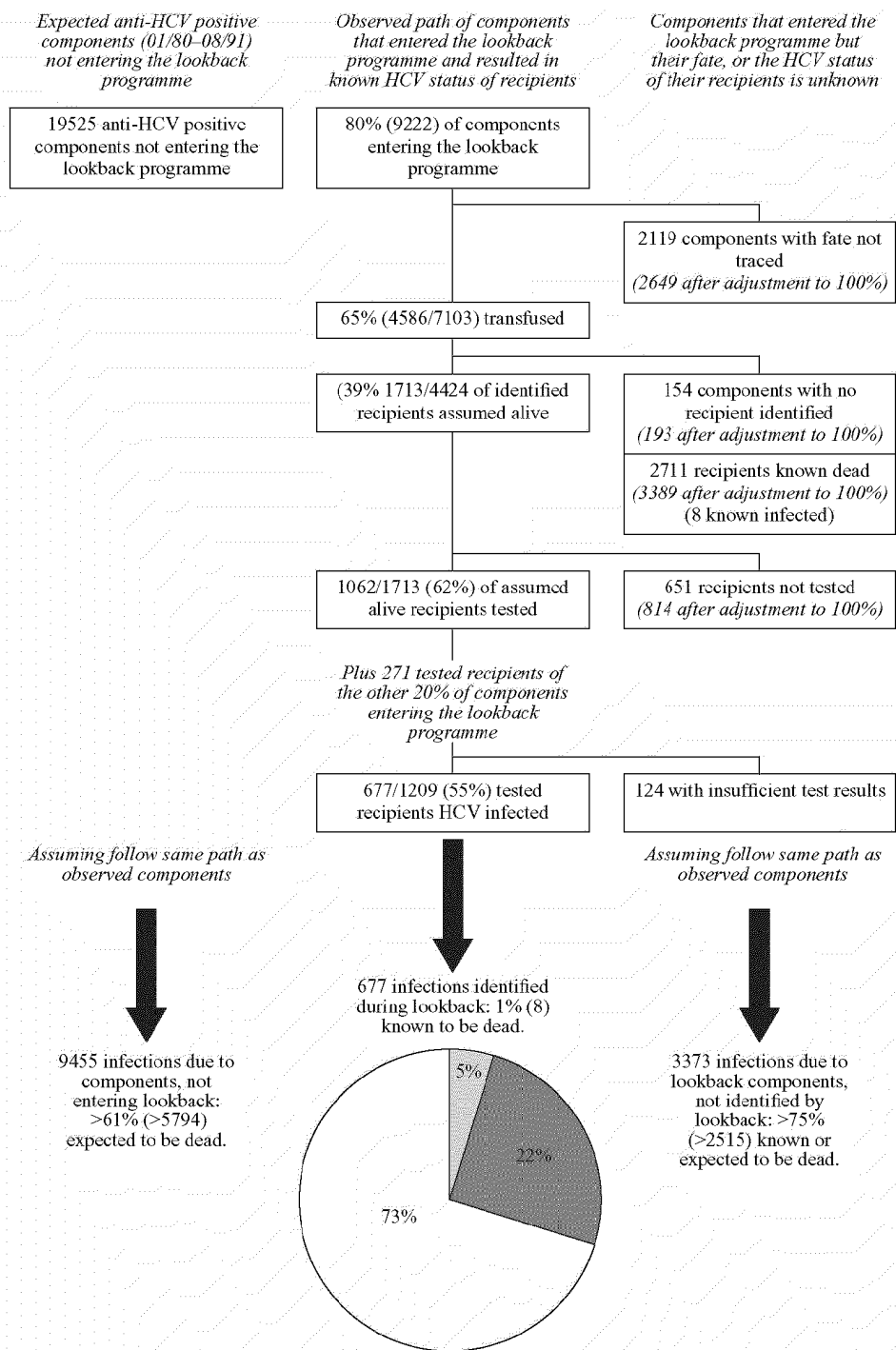
5%

22%

73%

Fig. 1. Total estimated transfusion-transmitted HCV infections (01/80–09/91). N = 13 500; < 5200 assumed alive in 1995.

in recipients who declined testing (i.e. 814 × 0·55). Of these infections, 1870 (55%) were known to be dead and an additional 19% (645) were expected to have died (based on applying the proportion observed to be known dead to those with unknown status) by the end of 1995. The median age of the identified recipients in this category in 1995 was 73 years.

A total of 25 864 035 donations were collected over the period 1 January 1980 to 1 September 1991, including an estimated 17 086 anti-HCV-positive donations.

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If, as observed for the lookback-programme 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 programme is uncertain. Of all components entering lookback, 9756 were collected between 1 January 1980 and the start of anti-HCV testing. If we assumed that all these lookback components were anti-HCV positive, then they constituted 37 % (9756/26 646) of the estimated total number of anti-HCV-positive components issued during this time period, and the remaining 16 890 (63 %) anti-HCV-positive components did not enter the lookback programme. Entry of these extra anti-HCV-positive components into the path would predict an extra 10 905 transfused recipients, and an extra 6034 IICV-infected recipients of which 3681 would be 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 confirmed anti-HCV-positive donors have been found to be HCV RNA-positive by PCR. Therefore, if we assume that only HCV RNA-positive donations transmit HCV infection, we would expect 75 % of anti-HCV-positive components to transmit. We observed that only 55 % of lookback components resulted in HCV infection, and this was used to estimate that only 73 % of the components that entered the lookback programme were anti-HCV positive ($0.73 \times 0.75 = 0.55$). The remaining 27 % of lookback donations where presumably collected while the donor was anti-HCV (and HCV RNA) negative. Using this adjustment resulted in an estimated extra 19 525 [$= 26 647 - (9756 \times 0.73)$] anti-HCV-positive components issued after 1 January 1980 that did not enter the lookback programme. The entry of these extra anti-HCV positive components into the path – with the use of a 0·75 probability of infection transmission for these components (i.e. the observed proportion of anti-HCV-positive donations also positive for HCV RNA) – predicted an extra 12 606 ($19 525 \times 0.65$) transfused components, and an extra 9455 ($12 606 \times 0.75$) HCV-infected recipients of which at least 5794 (9455×0.61) are expected to have died by the end of 1995.

In total, we therefore estimated that there have been approximately 13 500 HCV infections transmitted by HCV-infected blood components issued between 1 January 1980 and 1 September 1991. Over 8300 (61 %) of these were either known or expected to have died by the end of 1995.

DISCUSSION

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

We estimate that the HCV lookback programme has identified about 5 % (677) of the total number of HCV infections transmitted by transfusion from 1 January 1980 to 1 September 1991, and over 13 % of infected recipients who survived to 1995. It has been estimated that there are between 200 000 and 400 000 HCV-infected individuals living in the United Kingdom [2]; if this is so, transfusion since 1980 appears to account for between 3 and 7 % of all infections. Laboratory reports of HCV infection, that 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 6 [3].

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

Other analyses of data from the lookback programme [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 who did not donate after September 1991) not included in the lookback programme were collected and transfused previously – 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 estimates of assumed living transfusion-transmitted infections (in 1995) is therefore a maximum estimate.

We may have underestimated or overestimated the infections transmitted from 1 January 1980 to 1 September 1991 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, prohibited including earlier years. If the prevalence of anti-HCV amongst blood donors during the 1970s was assumed to be the same as at the end of 1991, inclusion of the 1970s data would generate approximately 10 000 extra HCV-infected blood recipients. As with estimates for the 1980s, over 61 % of these would be expected to have died by 1995 – probably well above this figure considering the greater average age of these recipients. If the average age of transfusion has stayed fairly constant over the years, 60 % of these recipients infected during the 1970s would have been born prior to 1920, i.e. would have been at least 75 years old by 1995.

These estimates may be useful for predicting the burden of HCV-related disease, or for assessing how the demand for HCV-related care compares to the burden of infection, particularly amongst the current older age groups that are expected to include a relatively large proportion of these transfusion-transmitted infections.

Only two transfusion-transmitted HCV infections have been reported from anti-HCV-tested components during the past 6 years [4] (up to the end 2001), and the risk of infection by transfusion has been reduced further by nucleic acid testing of blood donations. Transfusion-transmission of HCV in the United Kingdom 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].

REFERENCES

1. The 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 2002; **42**: 1146–53.
2. Booth JCL. Chronic hepatitis C: the virus, its discovery and the natural history of the disease. J Viral Hep 1998; **5**: 213–22.
3. Ramsay ME, Balogun MA, Collins M, Balraj V. Laboratory surveillance of hepatitis C virus infection in England and Wales: 1992 to 1996. Commun Dis Public Health 1998; 1: 89–94.
4. Asher D, Atterbury CLJ, Chapman C, et al. Serious Hazards of Transfusion (SHOT). Annual Report 2000–2001, 2002. ISBN 0953278948.
5. Harris H, Ramsay ME, Heptonstall J, Soldan K, Eldridge KP. The HCV National Register: towards informing the natural history of hepatitis C infection in the UK. J Viral Hep 2000; **7**: 420–7.