

Expert Report to the Infected Blood Inquiry: Statistics Group (Supplementary)

July 2023





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Introduction

Towards the end of the hearing regarding the Statistical Expert Report to the Infected Blood Inquiry on 9 November 2022, two questions were raised. Firstly, Ms Richards KC invited us to make recommendations about how data collection could be improved,¹ and secondly, Sir Brian Langstaff asked for our advice on overall mortality attributable to contaminated blood and blood products.² This document represents the response of the group to those two questions.

It is worth restating what was said in the Introduction to the Statistical Expert Group's (SEG's) original Report:

"It is important to be clear about the limitations of what we can conclude from this, and indeed any other, statistical investigation. In brief, any conclusions we draw from data will depend on:

Availability: sometimes the information we want was not collected or not retained.

Definitions: the numbers depend crucially on the criteria in use at the time, for example, what is meant by an antibody-positive HCV test has varied considerably over time.

Quality: data may not be accurate, particularly when part of routine collections rather than a planned study.

Completeness: data may be missing for a variety of reasons – and sometimes the fact that data are missing may itself be informative.

Context: for example, we need to take into account why the data were collected (for example, by review of death certificates; or at autopsy), and what was known at the time.

Skill in Interpretation: statistics are sometimes represented as hard 'facts', but the caveats listed above should make it clear that they can be much 'softer' than perhaps perceived. Drawing conclusions from data is not some automatic process, and judgement is always required – the data do not speak for themselves.

As explained previously, we try to be clear about these concerns by not only reporting numerical ranges expressing uncertainty about quantities, but also judgements on our confidence that the available data can answer the primary questions of interest.

An important limitation is that statistics are always an imperfect representation of what we are actually interested in. Tables and graphs of numbers of people infected and their subsequent survival are inevitably a gross, even harsh, summary of the suffering endured by those individuals and the people close to them. We provide no measures of illness, psychological distress, financial harms, family stress, and the many other ways in which infected blood will have damaged lives. In particular, we do not attempt to estimate onward-transmission to partners, children or others. We hope that readers will recognise our understanding that,

¹ Transcript 9 November pp174-178 INQY1000258

² Transcript 9 November pp182-195 INQY1000258

beneath all the counts and measurements, there are individual human lives. But it is only by summarising all those experiences into bald numbers that we can properly assess the magnitude of what has happened.”

The second question asked – the overall mortality attributable to contaminated blood and blood products – is particularly challenging to answer for the reasons outlined above. The true cause of death may be uncertain. For a death to be attributable to infected blood, it has both to be recognised as such and be described clearly. Overall, there are limited data of uncertain quality, with no clear classification indicating death due to infected blood and so care is required in interpretation. In addition, a significant proportion of the total number of deaths (deaths due to HCV infections from blood transfusions) comes from statistical modelling rather than counting cases of interest from databases. This adds uncertainty due to the assumptions necessary in the models.

We hope it is clear from what we said at the hearing, we are fully aware that we are not simply manipulating numbers. We are dealing with tragic events, and while we try to be as careful as we can, there will still be substantial uncertainty in the numbers presented. It is important to acknowledge the considerable uncertainty around the central estimates, due to the unavoidable limitations in our knowledge.

Sheila Bird, Stephen Evans and David Spiegelhalter on behalf of the Statistics Expert Group (SEG).

Q1 – SEG Recommendations on How Data Collection Could Be Improved

On 9 November 2022 towards the end of the Statistics Expert Group panel hearing, Ms Richards KC invited us (members of the Statistics Expert Group) to make recommendations “about how data collection could be improved”.

All nine UK-affiliated group members (authors of the *Expert Report to the Infected Blood Inquiry: Statistics*) recorded their priorities independently. Each of the 12 recommendations had high or medium support by two-thirds of the nine appraisers. Seven recommendations (asterisked) were rated high by six or more respondents.

The cost and likely cost-effectiveness of our recommendations are for others to appraise, although in practice it is challenging to assess the benefits of precautionary measures, including better information.

No international comparisons are made other than to remark that record-linkage across health, social care, education and prison registers is greatly facilitated in countries such as Sweden and Denmark which assign a personal number at birth.

SEG Recommendations in Assigned Priority Order

All nine UK-affiliated group members (authors of the *Expert Report to the Infected Blood Inquiry: Statistics*) recorded their priorities independently. Each of 12 recommendations was supported (high or medium) by two-thirds of the nine appraisers. Recommendations are summarized in the resulting priority order. Appraisers did not take the cost of implementation or cost-effectiveness into consideration.

TWELVE RECOMMENDATIONS in assigned priority order	Assigned priorities			
	High	Med	H+M SUM	Low
Alerts				
Persons with a bleeding disorder who were first treated in UK before 1992: to be alerted to ask to be Hepatitis C Virus (HCV) antibody tested if unsure about their HCV-status	9*		9	0
Three surviving subgroups who were transfused in UK before 1 September 1991 (defined by age-band at 31 December 2014): to be alerted to request an HCV antibody test if unsure about their HCV-status	8*	1	9	0
Linkage of a patient's transfusion usage and blood product usage to the patient's general practice electronic health record	6*	3	9	0
Transfusion Medicine				
Historical prevalence assessed via stored donor serum bank	6.5*	2.5	9	0
5-yearly transfusion-cohorts followed by record-linkage	6*	2	8	1
In event of a new transfusion-transmitted infection which may transmit sexually and/or mother-to-child, early consideration to be given to testing and assessing the impact on partners, children & parents	5	3	8	1
National Haemophilia Database of the UK Haemophilia Centre Doctors' Organisation (UKHCDO)				
Rigorous, adequately funded and statistician-supported National Haemophilia Database for persons with a bleeding disorder: as for those who receive donated organs	6.5*	2.5	9	0
National Services: such as UK Health Security Agency (UKHSA), national Blood Services, UKHCDO				
Those who are newly diagnosed with new blood-borne infection to be asked about receipt or donation of blood/tissue: using nationally agreed questions	6*	2	8	1
Enable better cross-referencing between databases, for example via no-names master-index, Community Health Index or National Health Service number	4	4	8	1
The history of epidemics should not be overlooked by reporting on the past 10-years only	4	3	7	2
Additional evidence of potential use to Funds				
Best-science typically requires access to a relevant post-exposure blood/tissue sample	2.5	4	6.5	2.5
Database(s) on funded-claimant-cohorts should be properly managed, such as to scientific standards, and analysable	2	4	6	3

Seven of the 12 recommendations were rated **high** by 6 or more respondents, as follows: all three recommendations on **Alerts**; two of three recommendations on **Transfusion Medicine**; together with recommendations on: those newly diagnosed with a blood-borne infection being asked about receipt or donation of blood/tissue; and on the need for rigorous, adequately-funded and statistician-supported National Haemophilia Database for persons with a bleeding disorder (PwBDs) as for those who receive donated organs.

Alerts to the public and/or Dear Doctor letter alerts to GPs

1. **Persons with a bleeding disorder who were first treated in the UK before 1992 should request a test if unsure about their HCV-status:**

If any such patients are not completely sure about having already tested HCV antibody negative, please ask your GP for an HCV antibody test so that there is no doubt. [NB Salivary HCV testing is less sensitive but is an option which avoids needle-stick should the patient so wish.]

2. **The *Expert Report to the Infected Blood Inquiry: Statistics* highlighted three high-risk sub-groups who received an HCV-infectious blood transfusion and who, were they to be diagnosed - even now - as chronically HCV-infected, could benefit from directly acting antiviral therapy.**

Comparison between the age-sex bands for England's claimants (registered with financial assistance schemes) who were HCV-infected by transfusion and alive at 31 December 2014 with the Statistics Expert Group's (SEG) estimated chronically HCV infected survivors for England identified three sub-groups who may benefit from being alerted:

2.1 ***Males and females who were aged 30-39 years at 31 December 2014 [and so born 1975 to 1984] who had received transfusion(s) during 1975 to August 1991 – essentially as a child:*** Median stochastic estimates for England are that male chronically HCV infected survivors outnumber females by 220: 120 (total of 340). Haematological cancers and chromosomal abnormalities may be dominant reasons for their having received transfusions in childhood. **Claimants are at best one-quarter of those expected by stochastic simulation.**

2.2 ***Males and females who were aged 40-49 years at 31 December 2014 [and so born 1965 to 1974] who had received transfusion(s) during 1970 to August 1991 – essentially as a child or young adult (up to 26 years of age):*** Median estimates are that male and female chronically HCV infected survivors are similar in number (total of 370) but that **only one-third feature as a claimant.** The reasons for transfusion may be different between the sexes as female survivors may have received transfusion in association with pregnancy.

2.3 ***Pregnancy will be a predominant reason for female survivors who were aged 50-69 years at December 2014 [and so born 1945 to 1964] to have received HCV-infectious transfusion(s) during 1970 to August 1991:*** Just over half (54%) of 860 such females, as estimated by stochastic simulation, feature as claimants.

3. **Linkage of a patient's transfusion usage or blood product usage to the patient's GP electronic health record, akin to a vaccine passport, could help patients and their general practitioner to keep track.**

Transfusion medicine

4. ***Historical prevalence of blood-borne infections to be assessable on representative stored residual samples per donation:***

Currently, donor blood samples and pre-transfusion recipient samples are stored for a short period post-transfusion to facilitate the investigation of short-term transfusion-related hazards only.

Representative, long-term storage of residual samples per donation did not occur during 1970-1991 so that when a new blood-borne virus was identified (HIV; HCV) and an antibody test was subsequently developed by which to protect the blood supply, the historical prevalence among blood donors of a virus such as HCV with a long incubation period to clinical disease could not be determined empirically.

There is no guarantee against the UK's blood supply being threatened again by a novel blood-borne virus which, like HCV, has a long incubation period to clinical disease.

But a well-designed system for long-term storage of representative residual samples per donation would allow the historical prevalence of a new virus to be determined efficiently.

[Possible methodology: Select four weeks at random each year (say, one week chosen at random per 13-weeks per calendar-year) with all residual samples to be stored from each blood donation in the randomly sampled weeks.

Each residual sample would have associated with it a brief demography about the donor (age in completed years at donation, sex, NHS region, country of birth as UK versus non-UK).

Such a serum-bank, of representative residual samples per donation, would - in the future - enable the UK to monitor the historical prevalence in blood donors of any new virus which is discovered to be transmissible in blood and is testable-for in the stored no-names samples.]

5. ***5-yearly calendar-year cohorts of transfusion-recipients to be followed-up for mortality via record-linkage for up to 20 years post-transfusion:***

Such cohorts enable two objectives:

5.1 **To monitor the use of transfusion** (for example, for whom - by age, sex, hospital where transfusion occurred, number of red blood cell units transfused, whether any other type of unit was also transfused and ICD10 discharge-code for the hospital-attendance when the index transfusion was administered).

5.2 **To compare, between 5-yearly cohorts, the influence of demography, transfused units and underlying disease on patients' survival in distinct epochs of follow-up** (such as 1st 4-weeks, rest of 1st year, rest of 1st 5-years, 2nd 5-years, 2nd decade).

6. ***In the event of a new transfusion-transmitted infection which may be transmitted sexually or from mother to baby:*** Early consideration should be given to testing to establish secondary infections and to assessing by record-linkage the impact on the morbidity and mortality of parents, partners and children by inviting their participation in a research-cohort which could also include in-person follow-up at a frequency that is constructive without being intrusive.

UKHCDO's National Haemophilia Database (NHD)

7. **Rigorous, adequately funded and statistician-supported National Haemophilia Database should be in place for patients with bleeding disorders**, as it is for patients who have undergone organ transplantation. Such support enables rigorous, timely analysis of patients' mortality and morbidity, on which new management policies or treatments undergoing randomized controlled trial (RCT) may impact.

On-study and follow-up forms (or data-screens) need to be designed to RCT-standards to ensure a high standard of completion with record-linkage to establish survival-status as a back-up, for example for patients who have been lost to follow-up.

UK Health Security Agency (UKHSA), Public Health Scotland (PHS), National Blood Services, UKHCDO

Since patients with bleeding disorders may, in future as in the past, be vulnerable to new transfusion-transmitted infections (new-TTI), **there needs to be better cross-referencing** between patients registered with UKHSA/PHS as having been diagnosed with new-TTI and donors or patients known to national Blood Services or UKHCDO as potentially at-risk. The detailed work of National vCJD Surveillance Unit in establishing whether a patient diagnosed as definite or probable vCJD had ever received (from whom) or donated blood/tissue (to whom) and the alerting of these vCJD-implicated persons illustrates what can be achieved - albeit for fewer than 200 vCJD cases.

8. **Patients who are newly-diagnosed with a blood-borne infection should be asked about their history of blood or tissue donation in the UK, and as a recipient of blood/tissue whether in or outside of the UK:** There needs to be UK-wide consensus on the framing of questions and how to pose them. Questions are posed in the public interest but will only benefit public health if asked in a manner which elicits frank answers.
9. **Master-indexing of respective registers is a no-names means of identifying which master-indices are shared between registers:** Conversations can then be had to verify if the same patient, or different patients, are associated with a master-index in common.

Master-index was defined as initial of first name, sounder of surname (e.g. B630 for Bird, Bard, Bert), sex, date of birth. Scotland's record-linkage is facilitated by its Community Health Index (CHI) numbers which, unlike NHS numbers, have a check-digit as a summation-guard against mis-typing.

10. **The UK's health security agencies should not distort their reporting on epidemics by focusing on recent-past events:** The history of epidemics should not be curtailed, and risk being forgotten about, by reporting only on the past 10 years especially when – as for HCV – transmission and progression occur over decades.

Additional evidence of potential use to Funds

11. ***Best-science when appraising claims requires that reasons to reject are well-documented and, ideally, claimants should provide a blood/tissue sample that is re-analysable as knowledge accrues:***

When a series of claims is dismissed on the same presumptive grounds of “no known infectivity” (for example, women with no other risk factors who were HCV-infected – they believed – by administration of infected anti-D intramuscular immunoglobulin in UK), the number of such dismissed claims may rise to an extent that warrants re-analysis – using best science - of the grounds for dismissal.

- 11.1 **Claimants and their doctor should be advised to locate (if possible) a residual stored blood sample taken soon after the claimant’s exposure; or for the claimant to provide (for storage) a blood sample at the time of submitting their claim.**

When a series of claims is dismissed on the same presumptive grounds, best science may include ***phylogenetics*** (ideally on a blood sample taken soon after transfusion) to establish historical clustering. However, once claimants have been diagnosed as chronically HCV infected and have received directly acting antiviral treatment to achieve sustained virological response, the potential of phylogenetics to identify historical clustering is gravely undermined. Hence, now and in the future, there is a need for claimants to register an early relevant blood sample.

- 11.2 **Persons with bleeding disorders who have been advised that they have been exposed to vCJD-implicated blood or blood products should, in life, consider giving consent for autopsy in the event of their death to establish if there is evidence of abnormal prion protein in lymphoid tissue.**

Chapter 6 of the SEG Report records that some post-mortems were carried out, one on the instruction of HM Coroner but such an instruction is not inevitable, as Chapter 6 also records. Post-mortem testing for the presence of the abnormal prion protein in lymphoid tissue is not only a means to establish the basis for an exposure-claim but also the only way in which evidence can be accumulated to revise the risk-assessment that those who survive have to live with to protect others.

12. ***Properly managed (to scientific standards) and analysable database on funded-claimant-cohorts would enable record-linkage follow-up for claimants’ mortality and for morbidity.*** Informed consent would be required if record-linkage were to access morbidity-information about surviving claimants such as the time-series of their hospitalisations.

Background Context

For effective surveillance of transmissible blood-borne diseases, “data collection” should ideally be interpreted to include the collection of a suitable biological sample by which to determine infection-status. For example, as chairman of the Medical Research Council’s Committee on Epidemiological Studies on AIDS, Professor Nick Day, determined that no study of risk behaviours for Human Immunodeficiency Virus (HIV) would be funded by the committee unless the proposed data collection included a biological sample that could be tested for HIV antibodies so that no-names linkage could be made between individuals’ risk-factor questionnaire and HIV-status.

We acknowledged that, in the late 20th century and thereafter, look-back was done well from patients who had died from variant Creutzfeldt Jakob Disease (vCJD) to establish their donation history and hence trace recipients of vCJD-at-risk donations; and also to alert as potentially vCJD-at-risk persons who had donated blood or tissue to a patient who subsequently developed vCJD. However, a low proportion (under 20%) of the persons thus alerted who subsequently died without having developed vCJD were subject to post-mortem to establish if abnormal prion protein (PrP^{Sc}) was present in their lymphoid tissue.

We also remarked that any database needs to be properly managed and analysable; and that it is not a trivial matter to get these things right. Particularly challenging is the proper management of data collected on a cohort of infected or at-risk persons when analysis of their survivorship from the date of infection is the goal. In general, date of infection is not known exactly and at-risk persons in the analysis cohort switch to “known to be infected” at their test-date, symptom-onset-date or death-date (if their infection-status was determined at or around the time of death, including by autopsy). In short, the data collected should include the date when infection was diagnosed. Moreover, if patients join an analysis-cohort only after infection was diagnosed, then their survivorship from infection to the diagnosis-date is a given (else the diagnosis would not have been made), and so – unless handled correctly at analysis – serious ascertainment bias can arise.

Finally, the *Expert Report to the Infected Blood Inquiry: Statistics* includes several examples of databases that were compiled under different auspices (disease surveillance, at-risk-exposure cohort, financial support for infected persons) but which related to some of the same patients. Added-value in terms of quantifying how many persons meet description X (for example: injector of heroin in the past year) can be gleaned from cross-referencing between databases A (drug misuse register), B (admissions to accident and emergency) and C (HCV register) to establish how many persons meeting description X feature in all three databases (ABC), how many in two of the three (AB, AC, BC) and how many on just one of the three. By making suitable assumptions, we can then estimate, for example, how many heroin injectors in the past year were missed by all three databases.

Individually unconsented, no-names record-linkage across databases requires that a strong case for public benefit has been made and that strong protection against deductive disclosure of individual identities is assured, see Goldacre Review (<https://www.goldacrereview.org/>) for a recent account of “trusted research environments”. Many permitted record-linkages – particularly to death-records, which are least contentious - have led to major discoveries about the public health. Discoveries range from the 1990s’ substantially higher risk of drugs-related death (~ 7 times higher) in the first fortnight following release from prison than at comparable other times at liberty to elegant record-linkage work during COVID-19 to estimate vaccine-effectiveness against different variants.

Q2 – Estimates of Overall Mortality Attributable to Infected Blood and Blood Products

How many deaths during 1970-2019 were caused by one or more of three blood-borne infections which were contracted by people transfused in the UK or by people with a bleeding disorder treated in the UK: Human Immunodeficiency Virus (HIV/AIDS), Hepatitis C virus (HCV), or variant Creutzfeldt Jakob Disease (vCJD/abnormal prion protein (PrP^{Sc}))?

Summary

1. Our estimates and intervals were based on analyses specified in the SEG Report, together with some further analysis, but necessarily included a substantial element of expert judgement concerning the impact of acknowledged limitations in the available data. Our estimates can therefore be considered as consensus judgements of the SEG.
2. A range of modelling options was considered, and the SEG scored these according to the plausibility of their underlying assumptions. The final results were based on combining the different options proportionally to the aggregate score given by SEG to each. These estimates are shown below, together with the estimates in the SEG report.

Group	Combined estimates by selecting proportional to aggregate scores	95% uncertainty interval	(SEG Report)
(a) HCV infections in transfusion recipients	1,640	550 to 3,440	1,820 (95% uncertainty 650-3,320)
(b) HIV infections in people with bleeding disorders	820	730 to 910	around half (625)
(c) HCV infections in people with bleeding disorders	350	255 to 590	no estimate (UKHCDO 248)
(d) HIV infections in transfusion recipients	35	32 to 40	no estimate (85% died, cause unknown)
(e) Diagnosed vCJD or carriage of abnormal prion protein in recipients of vCJD-implicated blood transfusion or blood products	5	3 to 8	3
Total	2,900	1,750 to 4,650	

Table 2.1 Estimates and 95% uncertainty intervals for total deaths attributable to infections, in five groups listed in decreasing order of the size of estimates.

3. SEG therefore concludes that around 2,900 deaths during 1970-2019 are attributable to infections from blood or blood products in the UK, although there is considerable uncertainty about this estimate. There are some changes from the estimates in the SEG Report, but these are not major given the inherent uncertainties.
4. There will inevitably be further deaths during 2020-2029, although their number will be mitigated by improved treatments for Hepatitis C virus and, on account of ageing, is likely to represent a lower proportion of all deaths during 2020-2029 than hitherto.
5. SEG recommends that record-linkage should continue to establish the date and cause of deaths during 2020-2029 from groups (b) and (c); and from UKHSA's key look-back study of traced cases and controls who had received an HCV-implicated blood transfusion prior to September 1991.

Introduction

1. In the *Expert Report to the Infected Blood Inquiry: Statistics* (the SEG Report), we provided estimates for the number of deaths that were attributable to infected blood or blood products within five groups, listed in decreasing order of the number of attributable deaths:
 - a) HCV infections in transfusion recipients (SEG Report, Chapter 4)
 - b) HIV infections in people with bleeding disorders (SEG Report, Chapter 1)
 - c) HCV infections in people with bleeding disorders (SEG Report, Chapter 2)
 - d) HIV infections in transfusion recipients (SEG Report, Chapter 3)
 - e) Diagnosed vCJD or carriage of the abnormal prion protein after receipt of vCJD-implicated blood or blood products (SEG Report, Chapter 6)
2. Some estimates were provided with ranges which were based on data from different sources, each with their limitations. We also provided an overall level of 'Confidence' that the available data could answer the question posed.
3. We consider only directly attributable blood-borne infection (BBI) deaths and do not include secondary transmission, which we acknowledge in the Introduction is an important limitation.
4. We have been asked to provide an 'unconditional' overall estimate, with accompanying uncertainty, that takes into account appropriate limitations and concerns. Our strategy has been:
 - To revisit the estimates in each of the five groups we consider, making use of any data that became available since we wrote the SEG Report.
 - By using different data sources and methods, to produce a list of possible options for the conclusions for each group. Each option is dependent on explicit assumptions, with corresponding conclusions expressed as an estimate and a plausible range.
 - There is no rigorous 'scientific' way to choose between these options, as the reasonableness of the methods and assumptions, and the reliability of the data sources, inevitably involve judgement. We therefore conducted a poll of the SEG members. For each of the five groups being considered, two to five possible options were discussed, and rather than simply choosing one of the options, UK-affiliated members of SEG were asked to assign scores to each option which added to 10: the higher the score, the greater the assigned credibility of that option. These scores were then added to produce an overall weight of support for each option. In this way, options believed by the group as a whole to be more likely, were weighted more heavily for the final estimates.
5. It is important to note that the total weighted estimate and 95% uncertainty interval are themselves summary statistics for a distribution representing the full uncertainty about the number of attributable deaths, which we show in **Figure 1** later in this document.

Analysis of 'well-defined' subset of the UKHCDO data

6. In order to carry out detailed survival analysis for people with bleeding disorders, a 'well-defined' subset of the National Haemophilia Database (NHD) was extracted. This comprised de-duplicated NHD-survivors who were born pre-1992, and first treated pre-1992 (or for whom the date of first treatment was missing), whose sex and age-band at 1 January 1992 were known and who were alive at 1 January 1992.
7. Analysis of survival within this dataset allowed, with additional statistical assumptions, estimation of hazard ratios summarising the additional risk entailed through being diagnosed as HIV/HCV or HCV alone. These additional risks are expressed as 'hazard ratios', meaning the increased risk of dying each year, relative to not being diagnosed with either condition. Applying these hazard ratios to the overall survival, in the manner used for the model for HCV infections in transfusion recipients (Chapter 4) provided estimates of the number of deaths attributable to infection (see Box below for further explanation). An additional complication was the need for hazard ratio estimation of the HCV-attributable deaths that occurred in persons with known exposure history but for whom HCV-test-status was not known within the NHD.
8. Comparison with the observed numbers of deaths that had been categorised as due to blood-borne infection provided an estimate for the additional deaths that were attributable to the infection, but whose cause-of-death had not been categorised as such.
9. Note that Tables in this Response are labelled Table 2.1, Table 2.2 etc., while Tables from the SEG Report are given their original label.

Explanatory Note on Hazard Ratios

Hazard ratios are used to summarise results of analysis of death rates. They can be used for other events than death, for example, progression rates, but the principles are the same.

When analysing death rates, we take account of how long people survive from a start-time, which is usually the time when follow-up began (for example their diagnosis date or recruitment date into a study or cohort of infected persons) when they are alive; and they are followed over time until they die.

Typically, we are interested in how death-rates vary over the course of follow-up. In particular, we may wish to compare death-rates in the first year of follow-up versus for those who have already survived for at least 5 years in the cohort.

To estimate the death-rate in the first year of follow-up, we count the number of people who die in that period, divided by the number of people who started their follow-up, each of whom contributes either a full-year (if they survived to the start of their 2nd year of follow-up) or a part-year (if they died within the 1st year or withdrew from the study for other reasons - such as emigration - during their 1st year of follow-up). This is a death rate per unit of time, also called a hazard rate.

A hazard ratio is the ratio of the hazard rate in two groups. One group is used as a reference (control or comparison group), sometimes an untreated group or people without a particular diagnosis and their hazard rate is used in the denominator of the ratio. The other group, one with that diagnosis, is then compared with the reference.

If, in the reference group, 100 deaths occur out of 10,000 persons followed for a year, then the death rate is 100 per 10,000 (or per 9,950 if deaths are assumed to have occurred half-way through the year). In the group **with** the diagnosis, suppose that 153 deaths occur, also out of 10,000 followed, then the ratio of these death rates, the hazard ratio (HR) is $153/100=1.53$.

A value of 1.0 for the HR indicates that the death rates in the two groups are the same. An HR greater than 1 suggests that the group of interest (**with** a diagnosis for example) has a higher death rate than the reference or control group. An HR of less than 1 suggests that the group of interest (**with** a diagnosis, for example) has a lower death-rate than the reference or control group.

From the example above, it can be seen that an HR of 1.53 can also be said to be a 53% increase in death rate.

While this can seem like an unnecessary complication when one could just give the death rates in the two groups, the hazard ratio is extremely useful in summarising more complex statistical analysis of death rates, or survival times, when adjustment has to be made for other explanatory factors (such as a bleeding disorder, co-infection, sex and age-group).

Adjusted hazard ratios can be used to estimate the number of deaths attributable to the risk factor of interest, in this case a diagnosed blood-borne infection. For example, if a diagnosis of chronic HCV infection is estimated to produce a hazard ratio of 1.53, and there are 100 deaths expected from other causes in those without a diagnosis, we would expect 153 in a similar group with the diagnosis of interest. We would therefore estimate that 53 of the total 153 were attributable to the diagnosis, meaning 35% ($53/153$) of all deaths are attributable to that diagnosis.

(a) People infected with HCV through blood transfusion in the UK between 1970 and 1991 who have died due to their chronic HCV infection

10. With Moderate confidence that the available data could answer the questions posed, the SEG Report (p38) provided the estimates shown below. These estimates were derived by a complex multi-stage probabilistic model, which featured many assumptions which are listed in the SEG Report. The focus is the final row of the table.

Quantity of Interest	Estimate	95% uncertainty interval
Number of people infected with HCV through blood transfusion between 1970 and 1991	26,800	21,300 to 38,800
Number chronically infected (were they to survive 6 months post-transfusion)	22,000	17,300 to 31,900
Number chronically infected who survived to 10 years after transfusion	8,120	6,330 to 11,900
Number chronically infected, and survived to end 2019 (assuming extra HCV risk)	2,700	2,050 to 3,910
Number chronically infected, and died by end of 2019	19,300	15,100 to 28,200
Number of deaths by end of 2019 related to HCV infection	1,820	650 to 3,320

Table 2.2 (S4 in SEG Report) Estimates and 95% uncertainty intervals of the main quantities of interest from the statistical model of HCV transmission from transfusions. Estimates are for the whole of the UK.

11. Reasons for adjusting the estimates in the final row of Table 2.2 (S4) include
- Of the many assumptions (a) to (k), listed on pages 41-42 of the SEG Report, sensitivity analysis suggests that one of the most influential is **Assumption (d) Self-deferral led to around a 67% reduction in donations from HCV-infectious ever-IDUs**. Assuming a smaller reduction of 33% (as suggested by some commentators) led to an estimate of 1,080 attributable deaths, a considerable reduction from the primary central estimate of 1,820 (Table 4.1, p44).
 - Assumption (k)** states that: *Chronic HCV infection increases the annual risk of dying from 10 years post-infection: our baseline assumption is a 53% increased risk*. This was derived from a case-control study covering more recent experience and represents treated natural history. It is feasible those HCV-infected through receiving transfusions in the 1970s had an increased hazard ratio due to lack of effective treatments, although since we do not, in general, expect attributable deaths within 10 years of HCV-infection, this may not have a major effect. We allow for increased HCV-attribution for those who survived 10 years after their HCV-infected transfusion in the 1970s by shifting the estimate for the hazard ratio from 1.53 (1.17 to 2.00) to the top-end of the confidence interval 2.00 (1.53 to 2.61) and thus the estimated attributable proportion of deaths from 35% to 50%. Allowing for this additional pre-1980 attributable mortality adds approximately 17% to the total number of attributable deaths.
12. Comparison with data from Funds (SEG Chapter 5) does not suggest systematic under-estimation.

13. Possible estimates for consideration by SEG, together with the scores ascribed to these options, are shown in Table 2.3, below. Comparing options A and B, we see that the results are extremely sensitive to the **Assumption (d)** about the effect of guidance in the mid-1980s for higher risk individuals to defer donations. While the SEG did not weight Option B highly, they did consider that a smaller effect was plausible.

Option	Description	Estimate	95% uncertainty interval	Total scores /70
A	Estimate in SEG Chapter 4	1,820	650 to 3,320	28
B	Allowing for smaller effect of guidance in 1980s (60% of Option A's central estimate)	1,090	390 to 1,990	9
C	Intermediate effect of guidance (80% of Option A's central estimate)	1,450	520 to 2,650	14
D	Allowing for increased hazard ratio of 10-year survivor after HCV-infection in the 1970s => 17% uplift in centrally estimated HCV-attributable deaths	2,130	760 to 3,900	19
Combining estimates by selecting proportional to scores		1,640	550 to 3,440	

Table 2.3 Options and combined estimates for total attributable deaths for HCV-RNA infected transfusion recipients

14. The combined estimate of 1,640 is then derived using a simulation method described in the box below. The accompanying 95% uncertainty interval is wide - from 550 to 3,440 - reflecting the substantial and unavoidable uncertainty arising from the modelling process.

Note on the simulation method used to obtain estimates for the total number of attributable deaths

For four Options (A to D), Table 2.3 shows estimates and 95% uncertainty intervals, which essentially summarise underlying uncertainty distributions. We aim to produce an 'average' of these distributions, appropriately weighted by the relative support for these Options provided by SEG. This is not a simple exercise that can be carried out using an explicit formula, and requires a more sophisticated simulation ('Monte Carlo') method, akin to that used in the SEG Report for HCV-infections from blood transfusions.

Total attributable deaths for HCV-RNA infected transfusion recipients

To estimate the total number of attributable deaths of HCV infected transfusion recipients, we begin with the estimates shown in Table 2.3.

Option A, used in the SEG report, gives an estimate of 1,820 deaths, although with considerable uncertainty around this value. The method draws numbers at random from a distribution centred on 1820 but such that 95% of the simulated values are between 650 and 3,320, the 95% uncertainty level in the table above (the precise form of the distributions is described at the end of this box).¹ Most values will be closer to 1,820, but more extreme values are also allowed to occur. 100,000 randomly sampled values are produced.

The same process is done for each of the other options, B, C and D: with randomly sampled values for each option, centred on 1,090, 1,450 and 2,130 respectively - this completes 100,000 'iterations' of the simulation.

Then, for each of the 100,000 iterations, an option is chosen at random, with chances proportional to the scores in the final column of Table 2.3. For example, to produce a combined estimate from the first iteration, the number generated assuming option A is chosen with probability of 28/70, the number generated assuming option B would be chosen with a probability of 9/70 and so on for each of the options. This process is repeated for each iteration, producing 100,000 possible values for the deaths resulting from HCV infection.

The median (middle value) of all 100,000 is then chosen as the combined estimate, with the corresponding uncertainty interval chosen to include 95% of the 100,000 weighted values for deaths from that infection.

The resultant distribution of values and its median, reflects the 'weight' given to each option based on the scores assigned by the SEG, and Table 2.3 shows a combined estimate of 1,640 with an uncertainty interval from 550 to 3,440. Note that the combined estimate is not simply the weighted mean (or median) of the estimates for each option, since it is the median of a skew distribution formed by essentially probabilistic weighting of other skew distributions.

This whole process is then repeated for each of the other groups, producing the estimates in Table 2.7, Table 2.10, Table 2.12, Table 2.13 and Table 2.14.

¹ **Distributional Forms Adopted** For those intervals that are symmetric around the central estimate, we assume a normal distribution with appropriate mean and standard deviation. For asymmetric intervals, we assume a 'split-log-normal' distribution: on the log-scale, this assumes a half-normal distribution on each side of the median, with standard deviation chosen to match the 2.5% of 97.5% values derived from the 95% uncertainty interval.

(b) People with bleeding disorders infected with HIV and HCV in the UK between 1970 and 1991 who have died due to their infections

15. The SEG Report (p8) provided the estimates shown below in Table 2.4, with Moderate/High confidence that the available data could answer the questions posed. The focus is on the final column of the table.

Sources	HIV diagnoses	Infected in the UK	Died by 2020	Died by 2020 of HIV-related causes
Macfarlane Trust	1,243	1,243	890 (72%) by 2013	Unknown
UK Haemophilia Centre Doctors' Organisation (UKHCDO)	1,338	Unknown but likely to be the great majority	1,017 (76%)	639 (48%)
UK Health Security Agency (UKHSA)	'Haemophiliac' 1,061 'Haemophiliac' + 'undetermined' 1,243	Unknown but likely to be the great majority	820 (77%) 963 (77%)	Unknown

Table 2.4 (Table S1 in the SEG Report) HIV diagnoses in people with bleeding disorders reported from three different sources up to the end of 2020.

16. Reasons for adjusting the estimates in the final column of Table 2.4 (S1) include:

- a) These patients were HIV/HCV co-infected, and so HCV-related deaths also need to be included. The date of HCV infection may have preceded that of HIV infection.
- b) HIV/AIDS on cause-of-death certificates ignores deaths linked to HIV that were not coded as such on the death certificate, and so would be an undercount.
- c) HIV-infection accelerated HCV-progression, and so both before and after the introduction of Highly Active Antiretroviral Therapy for HIV-disease and Directly Acting Antivirals for chronic HCV infection, HIV/HCV co-infected persons with bleeding disorder may have experienced HCV-related deaths which are not counted in Table 2.4.
- d) The number infected in the UK is unknown, although assumed to be the great majority.

17. (a) *HIV or HCV-related deaths*. The spreadsheet provided by UKHCDO provides the following causes of death among those diagnosed as HIV-infected:

HIV / AIDS	589
HIV related lymphoma	50
Hepatocellular carcinoma	13
Liver failure	0
Liver failure - HCV	131
Liver failure - other	1
Heart disease	23
Infection / multi-organ failure	17
Other causes	193
Total	1,017

This adds to $589+50+13+0+131 = 784$ HIV/HCV related deaths, comprising $784/1,017 = 77\%$ of all deaths, and $784/1,338 = 58\%$ of all those infected [Option A]. There were 40 deaths classified as heart disease or infection/multi-organ failure, making 824.

18. UKHSA provided further data on the cause of deaths, summarised in Table 2.6. There are 1,111 deaths reported, similar to the 1,017 recorded by UKHCDO. When combining 'Haemophilia' and 'Blood products (undetermined)', there are 376 'AIDS-related deaths', and a further 387 'cause of death not reported', which add to **763** [Option B].

	'Haemophilia'	'Other blood products'	'Blood products (undetermined)'	Total
'AIDS related deaths'	258	73	45	376
'Non-AIDS related deaths'	289	28	31	348
Cause of death not reported	273	47	67	387
Total deaths	820	148	143	1,111
Total cases	1,061	241	182	1,484

Table 2.6 Cause-of-death data for individuals infected by HIV through 'blood products' up to 2020.

19. The 'well-defined dataset' (see paragraph 6) contained **778** HIV/HCV deaths (494 after 1992), and **39** deaths categorised as heart disease or infection/multi-organ failure, making a total of **817** [Option C].
20. (b) *HIV/HCV deaths not labelled as such*. The approach based on the 'well-defined subset' is outlined in Section 2 of the **Appendix**. Hazard-ratio analysis estimated **569** (95% CI: 558 to 580) attributable deaths after 1992, compared to 523 by directly counting cause-of-death (including heart disease and infection/multi-organ failure). The ratio of these two, $569/523 = 1.09$ (1.07 to 1.11), suggests 9% additional HIV/HCV-related deaths labelled as other causes. Applying this factor to the 824 deaths of paragraph 17 gives an estimate of **898** (881 to 914) [Option D].
21. (c) *Allowance for infections abroad*. The final Inquiry judgement was around 1,250 HIV/HCV infections in the UK among people with bleeding disorders, representing around $1,250/1,338 = 93\%$ of cases. We could apply this factor to the estimates previously obtained.
22. Possible estimates for consideration by SEG, together with the scores ascribed to these options, are shown in Table 2.7.

Option	Description	Estimate	95% uncertainty interval	Total scores /70
A	Count of HIV/HCV categorised deaths from UKHCDO database - Allowing for only UK infections (~93%)	729 [93% of 784]		23
B	'AIDS-related deaths' and 'no cause of death reported' in UKHSA database	763		9
C	HIV/HCV, heart disease or infection/multi-organ failure from 'well-defined dataset;	817		14
D	Applying hazard-ratio analysis (+9%) to allow for uncategorised deaths	898	881 to 914	24
Combining estimates by selecting proportional to scores		820	730 to 910	

Table 2.7 Options and combined estimates for total attributable deaths for people with a bleeding disorder infected with HIV/HCV.

23. Option D provides a substantially higher estimate, but is based on many assumptions. In contrast, while the UKHCDO data have limitations, they are a clear minimum count. The SEG placed an almost equal weight on Option A and Option D. Overall Options C and D received more than half the scores, and so were influential in moving the estimate from 729 (A) to an overall **820**, based on the median simulated value.

(c) People with bleeding disorders infected with HCV, in the UK between 1970 and 1991, who have died due to HCV

24. The SEG Report (p2) provided the estimates shown below, with Low/Moderate confidence that the available data could answer the questions posed. The focus is on the final column of the table.

Source	HCV infections (without HIV)	Deaths
UKHCDO report	Confirmed ~2,400	~700 [39% from HCV-related causes]
	Additional 'possible' at least 2,400	~1,400
NHD	Well documented (i.e. both born & NHD-registered before 1992, & with record-linkage follow-up): 2,055	Before 2020: 536
Skipton Fund	~2,760	~900

Table 2.8 (S2 in SEG report) Number of HCV infections and deaths in people with bleeding disorders in the UK between 1970 and 1991: 'possible' infections include those known to have been exposed to at-risk blood products but with unknown HCV status. Additional infections will have occurred in those whose exposure history was unknown and who have not been tested for HCV.

25. Estimation of the number of attributable deaths presents a considerable challenge due to the large amount of missing data on both exposure and test history. Detailed commentary on these issues is provided in the Appendix.
26. The 'additional possible' of at least 2,400 infections shown in the Table 2.8 comprise those known to have been exposed but whose HCV status is unknown. If these patients had developed conditions related to HCV, they are likely to have been tested and moved category, and so it is plausible that there are few HCV-related deaths in this group.
27. Just as with people with bleeding disorders infected with HIV/HCV (Section (b)) we consider three approaches based on the UKHCDO data:
- the counts from the original UKHCDO report
 - counts from the well-defined dataset
 - survival analysis using hazard ratios
28. (a) *Counts from original UKHCDO report.* Tables of UKHCDO database provided to the Inquiry include 631 confirmed and presumed HCV-infected patients (without HIV) who have died, of whom 105 have died from 'Liver Failure HCV', 64 from other forms of Liver failure, and 140 have died from hepatocellular carcinoma (HCC) – see Table 2.6. This comprises $309/631 = 49\%$ of all deaths. In addition, there are 11 'liver-failure (other)' for those exposed but with unknown HCV status. A total of **320** attributable deaths may be reasonable [Option A].

	HCV +ve or presumed	Exposed but unknown HCV status
Hepatocellular carcinoma (HCC)	140	0
Liver failure	62	0
Liver failure – HCV	105	0
Liver failure - other	2	11
Heart disease	44	242
Infection / multi-organ failure	29	77
Other causes	249	1,056
Total	631	1,386

Table 2.9 Deaths in people with bleeding disorders with confirmed or presumed HCV infection, and those exposed but with unknown HCV status (Source UKHCDO)

29. *(b) Counts from well-defined dataset:* Well-defined counts of attributable deaths for confirmed HCV-infected: Hepatocellular carcinoma (HCC) + any liver-failure 192 (181 during 1992 to 2019, 11 pre-1992), infection and heart disease 61 (60 + 1), giving **253** [Option B].
30. *(c) Survival analysis from well-defined dataset:* See Sections 3 and 4 of the **Appendix** for details of these analyses which give us Options C, D and E.
31. Possible estimates for consideration by SEG, together with the scores ascribed to these options, are shown below. All estimates that are not counts are rounded to nearest 5.

Option	Description	Estimate	95% uncertainty interval	Total scores /70
A	Count of HCV-categorised deaths, and other liver failure in those untested, from UKHCDO database	320		16
B	HCV, heart disease or infection/multi-organ failure from 'well-defined dataset'; plus pre-1992 'otherwise well-defined' count of 12 (see Table 3.1 of Appendix)	253		6
C	Hazard-ratio analysis for those HCV infected or presumed HCV infected; plus pre-1992 clinical consensus count of 43 after inflation by 1.17 (95% CI: 0.90 to 1.38) to 50 (95% CI: 39 to 59), (See Appendix section 3)	290	240 to 340	11
D	Hazard-ratio analysis for those HCV infected or presumed HCV infected (ie 290 above), plus mid-option for those with unknown HCV status, adding 140 (95%CI: 36 to 220) HCV-related deaths in 2000-2019, (See Appendix section 4)	430	325 to 535	25
E	Hazard-ratio analysis for those HCV infected or presumed HCV infected, plus upper-option for those with unknown HCV status, adding 222 HCV-related deaths in 1992-2019, (See Appendix section 4)	510	360 to 665	12
	Combining estimates by selecting proportional to scores	350	255 to 590	

Table 2.10 Options and combined estimates for total attributable deaths from HCV infections in people with bleeding disorders.

(d) People infected with HIV through blood transfusions in the UK between 1970 and 1991 who have died due to HIV/AIDS

32. The SEG Report (p33) provided the estimates shown below, with Moderate confidence that the available data could answer the questions posed,

At least 79, and possibly up to ~100, people were infected with HIV through blood transfusions in the UK between 1970 and 1991, mostly pre-1986. Around 85% have subsequently died, but we do not know the causes of death.

A range of 20-40 deaths from HIV infection was discussed at the Inquiry.

33. Evidence that could provide a basis for estimating the number of attributable deaths includes the following.

- a) Unlike people with bleeding disorders infected through blood products, few of these transfused patients are likely to be co-infected with HCV if most of the infected donors were HIV-infected through being men who have sex with men (MSM). Hence, attributable deaths are likely to be HIV-related. For people with bleeding disorders infected with HIV/HCV, we estimate that 58% subsequently died from HIV-related causes.
- b) Many who receive transfusions die within a comparatively short period: for example, Table 4.11 (p73) of the SEG Report shows that only around half of those aged 50-59 years at transfusion will survive 5 years following the transfusion. Hence, we might expect fewer than 58% to die of HIV-related causes.
- c) Further data from UKHSA are summarised in Table 2.11 which show 32 'AIDS-related deaths' among those known to have been infected in the UK [Option A]. In addition, a proportion of those with 'cause of death not reported' may have died of conditions related to their HIV infection.
- d) However, those infected by HIV through transfusion are likely to have been detected by symptoms, and so it is likely that 'AIDS-related deaths' would have been recorded as such. We therefore set Option B as having a minimum of 32 known 'AIDS-related deaths', with a top end of the range at 40, and an estimate of 36.

	Acquired in UK	Acquired outside the UK	Country of infection not reported	Total
'AIDS related deaths'	32	37	4	73
'Non-AIDS related deaths'	10	17	1	28
Cause of death not reported	25	16	6	47
Total deaths	67	70	11	148
Total cases	79	137	25	241

Table 2.11 Diagnoses of those infected with HIV before the end of 2000 through exposure to 'other blood products', and subsequent deaths recorded up to the end of 2020. (Source UKHSA)

34. Possible estimates for consideration by SEG, together with the scores ascribed to these options, are shown below

	Option	Estimate	95 % uncertainty interval	Total scores /70
A	UKHSA count of 'AIDS-related deaths' among those known to have been infected in the UK	32		19
B	Allowing for additional HIV-related deaths	36	32 to 40	51
	Combining estimates by selecting proportional to scores	35	32 to 40	

Table 2.12 Options and combined estimates for total attributable deaths for HIV infections in transfusion recipients.

(e) People in the UK infected with vCJD from blood and blood products who have died from vCJD

35. The **SEG Report** (pages 92+93) states that there have been three vCJD deaths among persons who received a vCJD-implicated blood transfusion. The deaths occurred 6 years, 8 years and 10 years after transfusion from donors who subsequently developed vCJD.
36. The Transfusion Medicine Epidemiology Review (TMER) study reported that 31 vCJD cases were reported to be blood donors; an additional four vCJD patients were registered as potential donors with UK Blood and Transplant Service, only one of whom had given blood. Components from 18 of these 32 vCJD donors were issued to hospitals and given to 67 identified recipients; six further components are known to have been issued but could not be traced. Of these 67 individuals,
- Three – as described above – died on account of vCJD.
 - Thirty-four others died within 5 years of their vCJD-implicated transfusion: none is thought to have died from vCJD but none had post-mortem examination to look for abnormal prion (PrP^{Sc}) deposition in lymphoid tissue.
 - Eleven others died more than 5 years after their vCJD-implicated transfusion – but without post-mortem examination to look for PrP^{Sc} deposition.
 - Five further patients who died more than 5 years after their vCJD-implicated transfusion underwent post-mortem examination to look for PrP^{Sc} deposition, one of whom - an elderly woman who was heterozygous at codon 129 of the prion protein – was positive in her spleen for PrP^{Sc}.
37. In summary, vCJD (3) or PrP^{Sc} deposition (1) was evidenced in four out eight patients who received vCJD-implicated transfusion and who were subject to post-mortem. If either a 20%-rate (1/5) or a 50%-rate applied to the 11 others who died more than 5 years after their vCJD-implicated transfusion, then there might have been an additional 2 or 5 instances of PrP^{Sc} deposition.
38. Finally, disputed PrP^{Sc} deposition was identified in a 73-year old male with severe haemophilia who had been treated with vCJD-implicated Factor VIII and died in September 2009 with no history of neurological disease. His autopsy was performed under Her Majesty's Coroner's Instructions.
39. The SEG Report (pages 91+92) gives a brief account of over 5,000 persons with a bleeding disorder having been identified as “at-risk of vCJD for public health purposes”. Originally, when so advised by the CJD Incidents Panel, the implication was that their vCJD-risk had been estimated to be greater than 1%. Hence, those so advised needed to take precautions - including by alerting their doctor, dentist and surgeon – to protect the public health. Such persons were not asked to give permission-in-life for autopsy in the event of their death so that PrP^{Sc} deposition could be ascertained. Hence, post-mortem evidence to revise the original risk-estimate of 1% is lacking.
40. We note that there is age-dependent progression from dietary BSE exposure to clinical vCJD, which is reflected in the young age of vCJD cases, but the same need not apply to blood-borne transmission of the abnormal prion protein.
41. We note also that, in cattle surveillance, the prevalence of late-stage BSE in the brain of slaughtered adult cattle was three times higher in fallen stock than in healthy cattle presented for slaughter in the European Union. In humans, we do not know if PrP^{Sc} deposition presents an increased hazard for all-cause mortality.

42. Possible estimates for consideration by SEG, together with the scores ascribed to these options.

	Option	Estimate	95% uncertainty interval	Total scores /70
A	Confirmed cases in SEG Report	3		29
B	Allowance for additional cases in those who had received infected blood, and not been subject to appropriate testing at autopsy	5 – 8	5 - 8	41
	Combining estimates by selecting proportional to scores	5	3 to 8	

Table 2.13 Options and combined estimates for total attributable deaths for people who received vCJD-implicated transfusion(s) or blood products.

(f) Total attributable deaths

43. To obtain a total across all the primary infections, the 100,000 iterations for each infection group were added across groups, giving 100,000 weighted values for the total attributable deaths.
44. Had the values used as option A (a baseline model generally matching the SEG Report) for each infection been used, this would also give an estimate of 2,900 for the total. If instead, the single option with the highest score assigned by the SEG had been used, the overall total would be estimated to be 3,500. It is important to realise that the variation in the total obtained by various methods should not be seen as an issue, since there is such wide uncertainty.

Option	Rounded Estimates (nearest 50)	95% uncertainty interval
SEG (Option A)	2,900	1,750 to 4,400
Highest-scoring alternatives	3,500	2,100 to 5,300
Combining estimates by selecting proportional to scores	2,900	1,750 to 4,650

Table 2.14 Combined estimates for total attributable deaths due to infected blood or blood products in UK, 1970-1991

45. Figure 1 (below) clearly shows the substantial uncertainty associated with the total number of attributable deaths, which is inevitable given the lack of direct data on infection-status. The distribution shows that the two extremes of a 95% interval have limited support, whereas we would estimate 80% probability that the true total lay between 2,040 and 3,960.

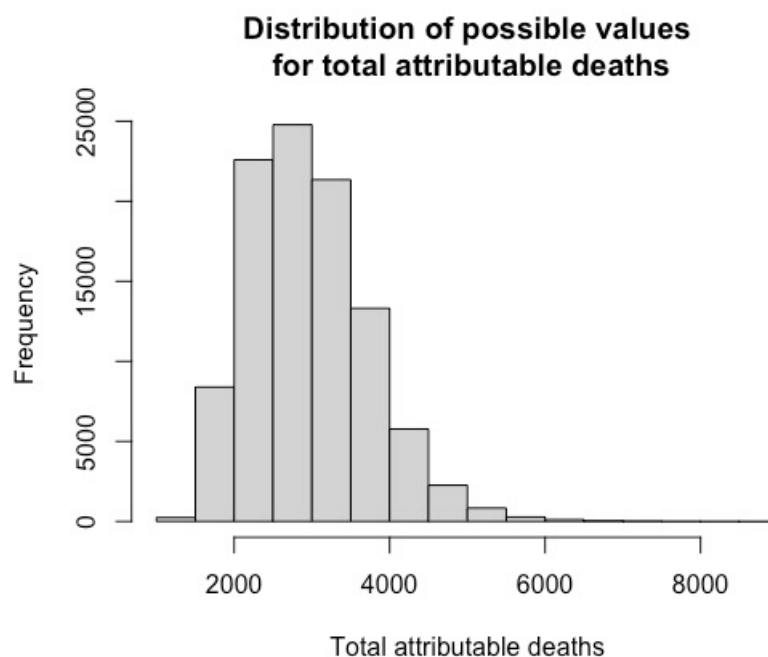


Figure 1 Distribution of possible values for the total number of attributable deaths, based on 100,000 simulations

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Verifying Statements

The standard verifying statement is as follows:

All contributing group members confirm that in respect of those parts of the report to which they have contributed:

- (i) They have made clear which facts and matters referred to in this report are within their knowledge and which are not.*
- (ii) Those that are within their knowledge they confirm to be true.*
- (iii) The opinions they have expressed represent their true and complete professional opinions on the matters to which they refer.*

Sections (i) and (ii) are somewhat unsuitable to statistical analyses, since we rely on data provided from a wide variety of sources, and so cannot say that the information we present is 'within our knowledge' or that we can confirm it to 'be true'.

However, we can confirm that we have exercised our best professional judgement as to the quality and interpretation of the evidence that was available.

Appendix

Analysis for estimates used in Q2(b) and Q2(c)

1. Introduction

Estimates (with 95% uncertainty intervals) are provided for three sub-groups in turn. The subgroups are:

1. HIV/HCV-infected persons with a bleeding disorder whose HIV-infection, for the most part, occurred during 1978 to 1986 (males predominate; one-third were HIV-infected as children: under 18 years of age), see **Section 2**;
2. Mono-HCV-infected persons with a bleeding disorder whose date of HCV-infection during 1970-1991 is, for the most part, unknown to the National Haemophilia Database (males predominate; 48% of 1,985 mono HCV-infected persons with a bleeding disorder who were alive at the start of 1992 were then aged 20-39 years), see **Section 3**;
3. Persons with a bleeding disorder in the **well-defined subset** (see below) who were exposed to HCV at-risk pooled plasma pre-1988 and/or to components pre-1992 but whose HCV-status was not known to the National Haemophilia Database, see **Section 4**.

We focused primarily on 6,282 patients in the slimmed National Haemophilia Database (sNHD3) well-defined subset of patients with a bleeding disorder, as shown in **Appendix Table 1.1**.

Well-defined means: known sex and age-band at 1 January 1992; born before 1992; first NHD-registered before 1992; date of 1st treatment before 1992 or missing; alive at 1 January 1992; known to have been exposed to pooled plasma products pre-1988 or to components pre-1992.

In the **well-defined subset**, 966/6,282 persons with a bleeding disorder were HIV/HCV co-infected.

Appendix Table 1.1: HIV/HCV status by HCV at-risk exposures

HIV/HCV status	Exposure to HCV at-risk products via				TOTALS
	Pre-1988 pooled plasma ONLY	Pre-1992 components ONLY	BOTH pre-1988 pooled plasma & pre-1992 components	Neither**	
HIV-infected	139	5	806	16	966
HCV-positive	631	146	1170	38	1985
HCV-negative	316	817	267	349	1749
At-risk but HCV-status Not Known	477	658	438	9	1582
TOTAL	1563	1626	2681	412	6282

** 'Neither' patients may, however, have been exposed to pooled plasma during 1988-1991

Accounting for persons with a bleeding disorder who were exposed to products that were at risk of transmitting HCV but whose **HCV-status was not known to NHD** requires the addition of further HCV-related deaths beyond those for persons who were **HIV-infected** (and assumed to be HIV/HCV co-infected) or who had been **diagnosed HCV-positive**. Moreover, pre-1992 blood-borne infection (BBI)-related deaths also need to be accounted for.

For each of the above subgroups, we provide a set of different central estimates (and associated 95% uncertainty interval) which reflect key judgements, and to which a sub-set of the authors may accord different credibility. We therefore elicited members' degree of belief in the scenarios per subgroup by inviting each member to assign scores which totalled to 10: the higher the score, the greater the assigned credibility.

2. HIV/HCV-infected persons with a bleeding disorder whose HIV infection, for the most part, occurred during 1978 to 1986 (males predominate; one-third were HIV-infected as children: aged under 18 years)

2.1 Basis for estimation: Estimation takes account of both HIV-related and HCV-related causes of death for HIV/HCV co-infected persons with a bleeding disorder. Estimation is based primarily on information from the National Haemophilia Database (NHD), the **well-defined subset** in particular, but cross-referenced to data made available by the UK Health Security Agency (UKHSA).

After covariate adjustment, the estimated HIV/HCV co-infection hazard-ratio (HR) for all-cause mortality during 2010-2019 allows us to derive the proportion [namely, (HR-1)/HR] of all deaths - experienced by HIV/HCV persons with a bleeding disorder in that decade - that was co-infection-related. We here rely on the same analysis framework as for mono-HCV-infected persons with a bleeding disorder (see below) although the estimated HR is higher for those co-infected. For example, the adjusted HR for HIV/HCV co-infected persons in 2010-2019 was **4.15** (95% CI: 2.86 to 6.02) versus **2.19** (95% CI: 1.72 to 2.79) for mono-HCV-diagnosed persons with a bleeding disorder (versus baseline: HCV-antibody negative persons with a bleeding disorder), **Appendix A, Table A.1**.

2.2 Unresolved problem: The date of HCV infection may have preceded the date of HIV infection for persons with a bleeding disorder who were HIV/HCV co-infected. Although HIV infections dated essentially from 1979 to 1986, HCV-infection dates may have been earlier than the earliest HIV-infection date of 1979.

2.3 How estimation proceeded: Switching missing HCV dates at 1 January 1992 or 1 January 2000 under-performed in terms of correctly retrieving epoch-specific hazard-ratios (HRs) during 1992-1999 and 2000-2009 for patients who were **HIV/HCV co-infected** for whom correctly-estimated HRs (versus those HIV-uninfected) were:

12.2 (95% CI: 10.1 to 14.8) in **Epoch 1** (1992 to 1999);

4.4 (95% CI: 3.4 to 5.7) in **Epoch 2** (2000 to 2009), reducing to

2.1 (95% CI: 1.5 to 2.8) in **Epoch 3+4** (2010 to 2019).

Their **Epoch 3+4 HR** (versus those HCV-antibody-negative) was **4.15** (95% CI: 2.86 to 6.02) using the covariate-adjustment in **Appendix A, Table A.1**.

For HIV/HCV co-infected persons with a bleeding disorder, **Appendix A, Table A.1** gives the adjusted HRs for **Epoch 3+4** (vs those HCV-antibody-negative) when adjustment is restricted to sex, age-band and bleeding disorder/severity. This adjustment accords with the sort of adjustment made in UKHSA's HCV-RNA-transfusion infected case versus control study.

In **Appendix Table 2.1** for **HIV/HCV co-infected persons with a bleeding disorder**, we summarize three inter-dependent sources for assessing blood-borne infection-related (BBI-related) deaths. The three sources are:

- i) UKHCDO PIVOT tables: pre-1980 and 5-yearly from 1980-84 to 2015-2019.
- ii) sNHD3 counts by clinical consensus including infection/multi-system disease and heart disease: pre-1992 and by epochs thereafter.
- iii) Based on HR-estimates applied to all-cause mortality during Epochs 1 and 2 (see above for 1992-2009) and in Epoch 3+4 from **Table A.1** (vs baseline of HCV antibody negative).

Appendix Table 2.1: Inter-dependent sources for assessing BBI-related deaths of HIV/HCV co-infected persons in UK with a bleeding disorder.

Epoch	Pre-1992	1992-1999	2000-2009	2010-2019	1992-2019	TOTAL
i) PIVOT tables with 40% of deaths in 1990-94 estimated [E] to have occurred pre-1992						
HIV/AIDS; HIV lymphoma	E271	E335	27	6	E368	639
HCC; any liver failure	E34	E59	42	10	E111	145
ii) sNHD3 clinical consensus: pre-1992 if date of 1 st treatment was pre-1992 or missing and, thereafter, by epoch for well-defined subset. Twelve HIV-infected persons with a bleeding disorder seemingly had 1 st treatment date after 1992 (who may have been HIV-infected outside of the UK or by maternal transmission).						
HIV/AIDS; HIV lymphoma	261	342	26	4	372	633
HCC; any liver failure	23	70	42	10	122	145
Infection/multi; heart disease	10 [3 + 7]	5 [0 + 5]	9 [6 + 3]	15 [7 + 8]	29	39
TOTAL	294	417	77	29	523	817
iii) sNHD3 well-defined subgroup: based on HR estimates applied to all-cause mortality during Epochs 1, 2 and 3+4 of 1992-2019 versus baseline of HCV-negative.						
All-cause mortality for those HIV/HCV co-infected		477	113	58	648	
Applicable HR (95% CI) for Epochs 1 & 2) or Appendix A.1 for Epoch 3+4		12.2 (10.1 to 14.8)	4.4 (3.4 to 5.7)	4.15 (2.9 to 6.0)		
Percentage of all deaths that are HIV/HCV-related is (HR-1)/HR (95% CI)		91.8% (90.1% to 93.1%)	77.3% (70.6% to 82.5%)	75.9% (65.5% to 83.3%)		
Applying the above percentage to all-cause mortality, estimated number of HIV/HCV-related deaths (95% CI)		438 (430 to 445)	87 (80 to 93)	44 (38 to 48)	569 (558 to 580)	Summed across Epochs: variance-sum = 32.1

For 1992-2019, the ratio of count iii) [**569 (95% CI: 558 to 580)**, by HR estimation] to count ii) [**523**, by clinical consensus] is **1.09 (95% CI: 1.07 to 1.11)**. This ratio suggests that the pre-1992 count ii) [**294**, by clinical consensus] *may warrant inflation* by 9% to **320 (95% CI: 314 to 326)**.

Based on **Appendix Table 2.1**, we propose three options as follows for BBI-related deaths of HIV/HCV co-infected persons in the UK with a bleeding disorder:

- A. **784 = 368** during 1992-2019 + **271** pre-1992 [via UKHCDO's PIVOT-tables for HIV/AIDS and **111** during 1992-2019 + **34** pre-1992 based on liver-related consensus codes for cause of death, both estimated by assuming that 40% of BBI-related deaths in the five years of 1990-1994 occurred pre-1992]
- B. **817 = 523** during 1992-2019 + **294** pre-1992 [via sNHD3, with addition of consensus codes for infection/multi-system disease and heart disease]
- C. **889 (95% CI: 876 to 902) = 569** during 1992-2019 (95% CI: 558 to 580) + **320** pre-1992 (95% CI: 314 to 326) [via HR estimated for all-cause mortality in distinct epochs of follow-up (1992-1999, 2000-2009, 2010-2019) plus inflation of pre-1992 consensus count ii) by 9% (95% CI: 7% to 11%) because HR estimation was 9% higher than count ii) during 1992-2019].

Notice that differences between options *are greater* than the width of the confidence interval for the computational option iii) in **Appendix Table 2.1**.

3. **Mono-HCV-infected persons with a bleeding disorder whose date of HCV-infection during 1970-1991 is mostly unknown to the National Haemophilia Database (males predominate; age-band at 1 January 1992 was 20-39 years for 947/1,985 (48%) mono HCV-infected persons with a bleeding disorder who were alive at the start of 1992, 509 of whom were then 20-29 years)**

3.1 Basis for estimation: Chronic HCV infection affects other organs besides the liver and so, lacking an HCV-RNA case-control study such as UKHSA's look-back study afforded for those HCV-infected via transfusion, estimation for mono-HCV-infected persons with a bleeding disorder has to rely upon proportional hazards regression analysis to account for other potentially influential covariates that could define the counterfactual for persons with a bleeding disorder (namely sex and age-band at 1 January 1992 together with bleeding disorder and its severity).

Having adjusted for these potentially influential covariates, the estimated HRs pertaining to HCV-status in a particular epoch, such as 2010-2019, then allows us to ascribe the proportion of all deaths in the epoch that are HCV-related as (HR-1)/HR.

3.2 Problems to be resolved in achieving estimation: First, the National Haemophilia Database (NHD) does not provide information on chronic HCV infection (HCV-RNA positive) as distinct from HCV antibody positivity. Hence, HCV-diagnosed and HCV-positive (without further specification) are here used interchangeably.

Second, HCV antibody testing to protect the UK's blood supply was introduced on 1 September 1991. Thereafter, based on presumed early outreach to potentially HCV-exposed persons with a bleeding disorder to offer counselling and HCV antibody testing, we might expect their known HCV test dates to cluster around 1991 and 1992. But they do not.

Third, the above presumption is not supported evidentially for two reasons: first, because HCV test dates are substantially missing from NHD (only one-sixth of HCV testees reported to NHD have recorded test dates); secondly, because 19% of HCV test dates that are recorded occurred in the 21st century. Hence, we cannot assume that HCV-status, as recorded on NHD, was already established by 1 January 1992 for persons with a bleeding disorder who were alive at 1 January 1992 and first treated before 1992 (ie potentially HCV-exposed).

The initial offer of HCV testing may have been declined, reporting of initial HCV test results to NHD may have been resisted, or inadequately recorded, or an HCV test offer was not made for a range of reasons: patient's age (young child), concern about properly informed consent, confidentiality, stigma, or clinical uncertainty about the longer-term implications of HCV infection and its treatment.

Fourth, and due to the above complication, in proportional hazards regression analyses we have to treat HCV-diagnosed and HCV-negative as time-dependent indicators which switch from zero to 1 at the patient's recorded HCV test date; alternatively, if the HCV test date is missing, the switch occurs at 1 January 2010. [NB: Switching all missing at 1 January 1992 or at 1 January 2000 gave still-biased answers for those HIV/HCV co-infected, who were our barometer.]

Fifth, for those chronically HCV-infected by transfusion, HR for all-cause mortality related to the calendar period 2000-2019 and was estimated from UKHSA's look-back study for traced persons who had received an HCV-implicated transfusion: HCV-RNA positive cases versus controls. Due to missing HCV test dates, the corresponding HR for all-cause mortality, as estimated by us for persons with a bleeding disorder who were HCV-diagnosed but HIV uninfected, relates to the calendar period 2010-2019. Hence, a judgement call is made in its application to 1992-2009 also, a judgement that appears reasonable in the light of the UKHSA analysis as precedent.

Sixth, as a further complication, HCV-status was not known at NHD for nearly 1,600 persons with a bleeding disorder who were considered to have been at-risk of HCV-infection due to exposure to pooled plasma pre-1988 or to components pre-1992. Not-known at NHD is not the same as not-known by the patient or haemophilia centre. Both calculation and **judgement** are required in assessing how many of these nearly 1,600 persons with a bleeding disorder whose HCV-status was not-known at NHD are indeed HCV-infected, see **Appendix B** and **Section 4**.

Judgement calls are supported by calibration of the HR-estimated proportion of all deaths as HCV-related against the UK Haemophilia Centre Doctors' Organisation (UKHCDO) consensus coding for cause of death.

Seventh, some HCV-related deaths may have occurred pre-1992 for persons with a bleeding disorder who were HCV-infected (but not HIV-infected), on which UKHCDO's consensus coding for causes of death pre-1992 sheds some light. The calibration referred to above is used to inflate (as necessary) the pre-1992 clinical consensus counts to account for HCV-related causes of death other than Hepatocellular Carcinoma (HCC) or any liver failure.

3.3 How estimation proceeded: For those persons with a bleeding disorder in the **well-defined** subset, the covariate-adjusted HRs for all-cause mortality during 2010-2019 according to HIV/HCV status are given in **Appendix A, Table A.1**.

Recall that even when NHD was aware that a patient had been either HCV-diagnosed or had tested HCV-antibody-negative, it holds an HCV test date for only one-sixth of those known by NHD to have been HCV-tested.

Recorded HCV test dates do not cluster around 1991 and 1992. Indeed, 19% of the 602 recorded HCV test dates occurred later than 1999.

Hence, two time-dependent indicators had to be defined which indicated respectively: when HCV-infection was diagnosed; when HCV antibody negative status was established. The respective indicators were switched-on (i.e. switched from zero to 1) at the patient's known HCV test date or - if HCV test date was missing - at 1 January 2010.

Sensitivity analyses – which entailed switching missing dates at 1 January 1992 or 1 January 2000 – under-performed in terms of correctly retrieving epoch-specific hazard-ratios (HRs) during 1992-1999 and 2000-2009 for patients who were **HIV/HCV co-infected** for whom correctly-estimated HRs (versus those HIV-uninfected) are as shown in **Section 2**.

In practical terms, missing HCV test dates meant that we could not rely upon HR-estimation for HCV-diagnosed persons in Epoch 1 (1992-1999) and Epoch 2 (2000-2009).

See **Appendix A, Table A.1** for adjusted HRs for **Epoch 3+4** (vs those HCV antibody negative) when adjustment is restricted to sex, age-band and bleeding disorder/severity. This adjustment accords with the sort of adjustment made in UKHSA's HCV-RNA-transfusion infected case versus control study – except that NHD records only those HCV-diagnosed without further specification to identify those chronically HCV-infected.

In **Epoch 3+4 (2010-2019)**, HR for **HCV-diagnosed** (versus HCV-antibody negative, see **Appendix A, Table A.1**) is **2.19** (95% CI: 1.72 to 2.79); and for **HCV-status not known** is **1.40** (1.08 to 1.81).

In **Appendix Table 3.1 for mono-HCV-infected persons with a bleeding disorder**, we summarize inter-dependent sources for assessing blood-borne infection-related (BBI-related) deaths. The three sources are:

- iv) UKHCDO PIVOT tables: pre-1980 and 5-yearly from 1980-84 to 2015-2019.
- v) sNHD3 counts by clinical consensus including infection/multi-system disease and heart disease: pre-1992 and by epochs thereafter.
- vi) Based on HR-estimation during Epochs 3+4 but applied to all-cause mortality during the Epoch 1, Epoch 2 and Epoch 3+4 of 1992-2019 versus baseline of HCV-negative.

Appendix Table 3.1: Inter-dependent sources for assessing BBI-related deaths of mono-HCV-infected persons in the UK with a bleeding disorder.

Epoch	Pre-1992	1992-1999	2000-2009	2010-2019	1992-2019	TOTAL
iv) PIVOT tables with 40% of deaths in 1990-94 estimated [E] to have occurred pre-1992 (first two rows include presumed HCV +ve in addition to HCV-diagnosed)						
HCC	E6	E21	43	63	E127	133
Any liver failure bar HCC	E37	E37	42	51	E130	167
Any liver failure bar HCC in HCV at-risk but NK-status	E5	E2	4	0	E6	11
Any liver failure bar HCC in "HCV not at-risk, presumed"	1	1	8	30	39	40
v) sNHD3 clinical consensus: pre-1992 if date of 1 st treatment was pre-1992 or missing and, thereafter, by epoch for well-defined subset: HCV-diagnosed						
HCC; liver failure-HCV	2 + 7 = 9	13+26 = 39	33+33 = 66	40+35 = 75	180	189
Any other liver failure	2	0	1	0	1	3
Infection/multi; heart disease	0 + 1 = 1	2 + 4 = 6	3 + 7 = 10	20+24 = 44	60	61
TOTAL	12	45	77	119	241	253
vi) sNHD3 well-defined subgroup: based on HR-estimates applied to all-cause mortality during Epoch 3+4 (2010-2019) also to all-cause mortality in Epoch 2 (2000-2009) versus baseline of HCV-negative.						
All-cause mortality for those diagnosed as mono-HCV-infected		66 + 2 (switches) = 68	117 + 3 (switches) = 120	255	443	
Applicable HR (95% CI) from Appendix A.1 for Epoch 3+4: applied also to Epochs 1 & 2			2.19 (1.72 to 2.79)			
Percentage of all deaths that are HCV-related is (HR-1)/HR (95% CI)			54.3% (41.9% to 64.2%)			
Applying the above percentage to all-cause mortality, estimated number of mono-HCV-related deaths (95% CI)		37 (28 to 44)	65 (50 to 77)	139 (107 to 164)	241 (208 to 274) Application of sum of variances = 275.5	241 (185 to 284) Application of HR 2.19 (95% CI) to 443 deaths

For 1992-2019, the **ratio** of count vi) [**241** (95% CI: 185 to 284), by HR estimation] to count v) [**241**, by clinical consensus] is **1.0** (95% CI: 0.77 to 1.18).

For Epoch 3+4 alone, wherein HR was formally estimated, the **ratio** of count vi) [**139** (95% CI: 107 to 164), by HR estimation] to count v) [**119**, by clinical consensus] is **1.17** (95% CI: 0.90 to 1.38).

This 2010-2019 ratio might suggest that the pre-1992 count iv) **43** by clinical consensus] **may warrant inflation** by 17% to **50** (95% CI: 39 to 59).

In summary, for persons with a bleeding disorder who were diagnosed as mono HCV-infected or were presumed HCV-infected, we posit a count of 241 + **50** = **291** (95% CI: 241 to 342) BBI-related deaths [**Option C** in Summary account in the main text].

4. Persons with a bleeding disorder in the well-defined subset who were exposed to HCV at-risk pooled plasma pre-1988 and/or to components pre-1992 but whose HCV-status was not known to the National Haemophilia Database.

Having set out in **Appendix Table 3.1** the available options for persons with a bleeding disorder who were HCV-diagnosed but were not HIV-infected, we then consider the contribution to BBI-related deaths that should be added to account for the HCV-infected subset within HCV at-risk persons with a bleeding disorder whose HCV-status is not known to NHD. The options are:

- a) **Zero addition** based on the assumption that chronic HCV disease, if present, would have become evident by 2019 [**Option C** in Summary account in the main text];
- b) **Mid-estimate** based on adjusted HR for all-cause mortality, as estimated during 2010-2019 for HCV at-risk persons whose **HCV-status is not known** to NHD [HR of **1.40** (95% CI: 1.08 to 1.81)] - but applied to deaths in Epoch 2 as well as to those in Epoch 3+4 [leading to **Option D** in Summary account];
- c) **Upper estimate** based on adjusted HR for all-cause mortality, as estimated during 2010-2019 for HCV at-risk persons whose **HCV-status is not known** to NHD - but applied to deaths in Epoch 1 & 2 as well as to those in Epoch 3+4 [leading to **Option E** in Summary account].

Accounting for persons with a bleeding disorder who were exposed to HCV at-risk products but whose HCV-status was not known to NHD may require the addition of further BBI-related deaths [**Options D and E** above].

Clinical consensus (see **Appendix A, Table A.2**) recorded their deaths from HCC, any liver disease or infection/multi system disease as 30, 40 and 25 in Epochs 1, 2 and 3+4 (**95 deaths**) plus a further 67, 61 and 25 deaths from heart disease (**additional 153 deaths**). We propose:

- A. **lower extreme** of **zero** additional BBI-related deaths is unlikely based on both clinical consensus and proportional hazards analysis [**zero** addition to **Option C** in Summary account];
- B. **mid-approximation**: application of HR of **1.40** in Epoch 3+4 (95% CI: 1.08 to 1.81) - which implies BBI-related percentage of $[(HR-1)/HR]$ or **28.6%** (95% CI: 7.4% to 44.8%) for **HCV-status not known** deaths - to that subgroup's all-cause mortality of 334 and 156 deaths respectively in Epoch 2 and Epoch 3+4 (total of **490 deaths**, see **Appendix A, Table A.3**) to estimate their associated BBI-related deaths as **140** (95% CI: 36 to 220) but with no attribution of earlier deaths as HCV-related [added to **Option C** to give **Option D** in Summary account];

- C. **upper extreme:** application of HR of **1.40** in Epoch 3+4 (95% CI: 1.08 to 1.81) - which implies BBI-related percentage of $[\text{HR}-1]/\text{HR}$ or **28.6%** (95% CI: 7.4% to 44.8%) for **HCV-status not known** deaths - to that subgroup's all-cause mortality of 281, 334 and 156 deaths in Epochs 1, 2 and 3+4 respectively (total of **771 deaths**) to estimate their associated BBI-related deaths as **221** (95% CI: 57 to 345) but with no attribution of earlier deaths as HCV-related [added to **Option C** to give **Option E** in Summary account].

Take-home message from Sections 3 & 4: Mono-HCV-infected persons with a bleeding disorder (diagnosed and HCV-status not known) contribute an **upper estimate** of **510** (95% CI: 360 to 665) BBI-related deaths to end 2019 [**Option E** in Table. 2.10 of this report], a **mid-approximation** of **430** (95% CI: 325 to 535), BBI-related deaths to end 2019 [**Option D** in Table. 2.10 of this report], and a **lower extreme** of **291** (95% CI: 241 to 342), BBI-related deaths to end 2019 [**Option C** in Table. 2.10 of this report].

For 1992-2019, the **ratio** of count vi) [**241 (95% CI: 185 to 284)**, by HR estimation] to count v) [**241**, by clinical consensus] is **1.0 (95% CI: 0.77 to 1.18)**. For Epoch 3+4 alone, wherein HR was estimated, the **ratio** of count vi) [**139 (95% CI: 107 to 164)**, by HR estimation] to count v) [**119**, by clinical consensus] is **1.17 (95% CI: 0.90 to 1.38)**.

This ratio might suggest that the pre-1992 count [v) **12** or iv) **43** by clinical consensus] **may warrant inflation** by 17% to **14** (11 to 19) or **50** (95% CI: 39 to 59).

Appendix A

Table A.1 EPOCH 3+4 only for well-defined subset: bleeding disorder/severity covariates fitted without exposure covariates; HRs for bleeding disorder/severity as proxy and to serve as counterfactual (NB: missing HCV-test dates switched at 1 January 2010)

COVARIATES	EPOCHS 3+4: 580 death (2010-2019, 10 years); HIV-status		EPOCHS 3+4: 580 death (2010-2019, 10 years); HCV-status	
	Hazard Ratio, HR	95% CI for HR	Hazard Ratio, HR	95% CI for HR
Gender (baseline: male)				
Female	0.69	0.49 to 0.95	0.67	0.48 to 0.93
Age-band at 31 December 1991 (baseline: 20-29 years)				
Under 20	0.51	0.33 to 0.79	0.54	0.35 to 0.83
30-39	1.74	1.28 to 2.36	1.74	1.28 to 2.36
40-49	3.57	2.66 to 4.79	3.69	2.75 to 4.96
50-59	8.3	6.2 to 11.2	9.1	6.8 to 12.3
60+ years	18.4	13.6 to 24.9	20.7	15.1 to 28.4
Bleeding Disorder Diagnosis & Severity (baseline: Haemophilia A ≤ 5 IU/dl)				
Haemophilia A other	1.06	0.85 to 1.33	1.18	0.93 to 1.48
Haemophilia B ≤ 5 IU/dl	1.22	0.88 to 1.70	1.17	0.84 to 1.63
Haemophilia B other	1.13	0.75 to 1.72	1.21	0.79 to 1.83
Von Willebrand disease	1.17	0.84 to 1.63	1.44	1.03 to 2.02
Any Acquired BD/Other	1.17	0.76 to 1.79	1.33	0.86 to 2.06
HIV-status (baseline = not known to be HIV-infected includes mono HCV-infected persons)				
HIV-antibody- positive	2.32	1.70 to 3.17		
HCV-status (baseline = HCV-negative at NHD)				
HIV-antibody- positive			4.15	2.86 to 6.02
HCV-positive			2.19	1.72 to 2.79
HCV-status NK			1.40	1.08 to 1.81

A.2 Consensus cause of death by epoch and HIV/HCV-status for persons with a bleeding disorder in the well-defined subset for proportional hazards (PH) analyses

Table A.2.1 Clinical consensus on cause of death by HCV status for deaths between 1992-1999 (EPOCH 1) with HCV status known as of 1992 [As in PH regression analyses].

NB: Unknown HIV/HCV status patients experienced: **97** heart disease, HCC, any liver failure, or infection/multisystem disease deaths [**30** if heart disease is discounted].

Clinical Consensus on Underlying Cause of Death	Unknown	Known HCV NEG	Known HCV POSITIVE	HIV	Total
1. Accidental death	1	0	0	0	1
2. Acquired bleeding	10	0	0	1	11
3. Bleeding - abdomen	0	0	0	3	3
4. Bleeding - chest	1	0	0	0	1
5. Bleeding – gastro	8	0	2	0	10
6. Bleeding – intracranial	48	0	7	30	85
7. Bleeding – other	3	0	0	0	3
9. Cancer – other	49	0	8	9	66
10. Creutzfeldt-Jakob					
11. Frailty/ dementia	8	0	2	0	10
12. HIV / AIDS	0	0	0	320	320
13. HIV lymphoma	0	0	0	22	22
14. Heart disease	67	3	4	5	79
15. Hepatocellular cancer	7	0	12	3	22
16. Infection / multi	11	0	2	0	13
17. Liver failure	10	0	0	0	10
18. Liver failure – HCV	1	0	25	67	93
19. Liver failure – other	1	0	0	0	1
20. Not known	3	0	0	6	9
21. Other medical disease	25	1	1	4	31
22. Overdose	3	1	0	1	5
23. Post-op complication	1	0	2	0	3
24. Ruptured aneurysm	6	0	0	1	7
25. Stroke: thrombotic	4	0	1	0	5
26. Suicide	8	0	0	0	8
27. Trauma	5	1	0	5	11
28. Venous thrombosis	1	0	0	0	1
TOTALS	281	6	66	477	830
SUB-TOTALS re BLEEDING	60	0	9	33	102
(as %)	(21.4)	(0.0)	(13.6)	(6.9)	(12.3)

Table A.2.2 Clinical consensus on cause of death by HCV status for deaths between 2000-2009 (EPOCH 2) with HCV status known as of 2000 [As in PH regression analyses]

NB: Unknown HIV/HCV status patients experienced: **101** heart disease, HCC, any liver failure, or infection/multisystem disease deaths [**40** if heart disease is discounted].

Clinical Consensus on Underlying Cause of Death	Unknown	Known HCV NEG	Known HCV POSITIVE	HIV	Total
1. Accidental death	4	0	0	1	5
2. Acquired bleeding	5	1	0	0	6
3. Bleeding - abdomen	1	0	0	1	2
4. Bleeding - chest	0	0	1	0	1
5. Bleeding – gastro	5	0	4	2	11
6. Bleeding – intracranial	54	3	9	15	81
7. Bleeding – other	4	1	0	2	7
9. Cancer – other	58	5	9	8	80
10. Creutzfeldt-Jakob					
11. Frailty/ dementia	14	1	1	0	16
12. HIV / AIDS	0	0	0	20	20
13. HIV lymphoma	0	0	0	6	6
14. Heart disease	61	1	7	3	72
15. Hepatocellular cancer	7	0	33	7	47
16. Infection / multi	27	2	3	6	38
17. Liver failure	3	0	0	0	3
18. Liver failure – HCV	0	0	31	35	66
19. Liver failure – other	3	0	1	0	4
20. Not known	11	0	3	2	16
21. Other medical disease	36	2	9	2	49
22. Overdose	5	0	0	1	6
23. Post-op complication	4	1	0	0	5
24. Ruptured aneurysm	3	0	1	0	4
25. Stroke: thrombotic	11	1	4	0	16
26. Suicide	8	0	0	2	10
27. Trauma	8	1	1	0	10
28. Venous thrombosis	2	0	0	0	2
TOTALS	334	19	117	113	583
SUB-TOTALS re BLEEDING	64	4	14	20	102
(as %)	(19.2)	(21.1)	(12.0)	(17.7)	(17.5)

Table A.2.3 Clinical consensus on cause of death by HCV status for deaths between 2010-2019 (EPOCH 3+4) with HCV status known as of 2010 [As in PH regression analyses]

NB: Unknown HIV/HCV status patients experienced: **50** heart disease, HCC, any liver failure, or infection/multisystem disease deaths [**25** if heart disease is discounted].

Clinical Consensus on Underlying Cause of Death	Unknown	Known HCV NEG	Known HCV POSITIVE	HIV	Total
1. Accidental death	1	0	5	0	6
2. Acquired bleeding	4	0	0	0	4
3. Bleeding - abdomen	0	1	1	1	3
4. Bleeding - chest	0	0	1	1	2
5. Bleeding – gastro	4	2	3	0	9
6. Bleeding – intracranial	9	4	26	9	48
7. Bleeding – other	0	0	1	2	3
9. Cancer – other	37	33	53	9	132
10. Creutzfeldt-Jakob	1	0	1	0	2
11. Frailty/ dementia	12	8	7	0	27
12. HIV / AIDS	0	0	0	2	2
13. HIV lymphoma	0	0	0	2	2
14. Heart disease	25	12	24	8	69
15. Hepatocellular cancer	8	0	39	2	49
16. Infection / multi	17	17	20	7	61
17. Liver failure					
18. Liver failure – HCV	0	0	33	8	41
19. Liver failure – other	0	2	0	0	2
20. Not known	3	3	11	1	18
21. Other medical disease	26	20	25	3	74
22. Overdose	1	1	0	1	3
23. Post-op complication	1	0	0	1	2
24. Ruptured aneurysm	1	1	0	0	2
25. Stroke: thrombotic	4	3	3	0	10
26. Suicide	1	1	1	1	4
27. Trauma	0	3	1	0	4
28. Venous thrombosis	1	0	0	0	1
TOTALS	156	111	255	58	580
SUB-TOTALS re BLEEDING	13	7	32	13	65
(as %)	(8.3)	(6.3)	(12.5)	(22.4)	(11.2)

Table A.3 All-cause mortality by epoch and covariate level: for simplicity, deaths are related to the covariate level that pertained initially, ie at entry to risk-set.

HCV-status switches during Epoch & deaths during Epoch for those switched are recorded in the extra final rows of the table.

COVARIATES	EPOCH 1: 830 deaths		EPOCH 2: 583 deaths		EPOCH 3+4: 580 deaths	
	6,282 persons at-risk		5,452 persons at-risk		4,869 persons at-risk	
	# initial risk-set	# deaths	# initial risk-set	# deaths	# initial risk-set	# deaths
Male	5230	783	4447	498	3949	484
Female	1052	47	1005	85	920	96
Age-band @ 31 December 1991						
Under 20	1462	79	1383	34	1349	32
20-29	1389	139	1250	63	1187	73
30-39	1251	150	1101	88	1013	97
40-49	981	127	854	100	754	130
50-59	559	102	457	101	356	125
60+	640	233	407	197	210	123
Bleeding disorder: diagnosis & severity @ 1992						
HaemA <=5	2246	534	1712	206	1506	171
HaemA other	1558	140	1418	154	1264	182
HaemB <= 5	494	32	462	53	409	48
HaemB other	292	26	266	26	240	28
VonWillebrand	1175	63	1112	97	1015	106
Any Acq/other	517	35	482	47	435	45
Exposure to components pre-1992						
YES	4370	706	3601	472	3129	454
No	1975	124	1851	111	1740	126
Exposure to pooled plasma						
Yes, pre-1988	4244	730	3514	440	3074	441
Yes, 1988-91	635	29	606	38	568	41
No	1403	71	1332	105	1227	98
HCV-status @ beginning of EPOCH						
HIV-infected	966	477	489	113	376	58
HCV positive	1739	66	1870	117	1796	255
HCV negative	1580	6	1688	19	1716	111
HCV-status NK @ NHD	1997	281	1405	334	981	156
HCV-status switches during epoch and associated deaths						
Switched to HCV positive	199	2	50	3	4	0
Switched to HCV negative	114	1	47	4	0	0
Switched out from HCV-NK	313	3	97	7	4	0

Appendix B

We focused primarily on 6,282 patients in the slimmed National Haemophilia Database (sNHD3) **well-defined subset** of patients with a bleeding disorder, as shown in **Table B1**.

Well-defined means: known sex and age-band at 1 January 1992; born before 1992; 1st NHD-registered before 1992; date of 1st treatment before 1992 or missing; alive at 1 January 1992; known to have been exposed to pooled plasma products pre-1988 or to components pre-1992.***

In the **well-defined subset**, 966/6,282 persons with a bleeding disorder were HIV/HCV co-infected.

Table B.1: HIV/HCV status by HCV at-risk exposures

HIV/HCV status	Exposure to HCV at-risk products via				TOTALS
	Pre-1988 pooled plasma ONLY	Pre-1992 components ONLY	BOTH pre-1988 pooled plasma & pre-1992 components	Neither**	
HIV-infected	139	5	806	16	966
HCV-positive	631	146	1170	38	1985
HCV-negative	316	817	267	349	1749
At-risk but HCV-status Not Known	477	658	438	9	1582
TOTALS	1563	1626	2681	412	6282

** 'Neither' patients may, however, have been exposed to pooled plasma during 1988-199

We assume that all who were HIV-infected were also HCV-infected and that their HIV-status took testing precedence. Hence, our interest focuses primarily on the association between exposure to HCV at-risk products (for those exposed) and whether the patient was HCV-tested.

Notice that, **when HCV-tested**, only a small percentage of the 387 HIV-uninfected HCV-tested persons with a bleeding disorder but with no known exposure were HCV-positive [38/387 or **9.8%** (95%CI: 6.8% to 12.8%)] and so, for the nine, apparently unexposed, who were not HCV-tested, we might expect **0.9 HCV-positives** (95% CI: 0.6 to 1.2).

For those exposed but not HIV-infected, having been recorded by NHD as HCV-tested is **not independent** of exposure type, see **Table B.2**. Patients with both exposure types were significantly more likely to be HCV-tested (1437 HCV-tested versus 1276 expected). The HCV-testing deficit was most marked for those exposed ONLY to pre-1992 components (963 HCV-tested versus 1103 expected).

Table B.2: HCV-tested by HCV at-risk exposure for those who were not HIV-infected

HCV-tested as known to National Haemophilia Database	Exposure to HCV at-risk products via:			TOTALS
	Pre-1988 pooled plasma ONLY	Pre-1992 components ONLY	BOTH pre-1988 pooled plasma & pre-1992 components	
HCV-tested	947 (expected: 969)	963 (expected: 1103)	1437 (expected: 1276)	3347
NK HCV-tested	477 (expected: 455)	658 (expected: 482)	438 (expected: 599)	1573
TOTALS	1424	1621	1875	4920
% HCV-tested (95% confidence interval)	66.5% (64.1% to 69.0%)	59.4% (57.0% to 61.8%)	76.6% (74.7% to 78.6%)	

The above differential HCV-tested rates according to HCV at-risk exposure-route [**66.5%** (95% CI: 64% to 69%) if exposed ONLY to pre-1988 pooled plasma; **59.4%** (95% CI: 57% to 62%) if exposed ONLY to pre-1992 components; but **76.6%** (95% CI: 75% to 79%) HCV-tested if exposed to **BOTH**] are only the first part of the story.

The second part is that, **when HCV-tested**, the HCV-positive rate is also different according to the HCV at-risk exposure-route, being **66.6%** (95% CI: 64% to 70%) if exposed ONLY to pre-1988 pooled plasma; **15.2%** (95% CI: 13% to 17%) if exposed ONLY to pre-1992 components; but **81.4%** (95% CI: 79% to 83%) HCV-infected if exposed to **BOTH**, see **Table B.3**.

When HCV-tested, all three HCV-positive rates seem to have been sufficiently high to have warranted comprehensive counselling and the offer of HCV antibody testing to those at-risk by any one of the three HCV at-risk exposure-routes.

Table B.3: When tested, HCV-test result by HCV-at-risk exposure for those were not HIV-infected

When tested, HCV-test result	Exposure to HCV at-risk products via			TOTALS
	Pre-1988 pooled plasma ONLY	Pre-1992 components ONLY	BOTH pre-1988 pooled plasma & pre-1992 components	
HCV-positive	631	146	1170	1947
HCV-negative	316	817	267	1400
TOTALS	947	963	1437	3347
% HCV-positive (95% confidence interval)	66.6% (63.6 to 69.6%)	15.2% (12.9 to 17.4%)	81.4% (79.4 to 83.4%)	

Not known to have been HCV-tested according to the National Haemophilia Database (NHD) is **not the same** as patients having never been HCV-tested. Moreover, the NHD may be more likely to be informed about HCV at-risk persons with a bleeding disorder who had tested HCV-positive than if the patient had tested HCV-antibody-negative.

We might therefore argue – **at one extreme** - that almost all HCV at-risk persons with a bleeding disorder will have been HCV-tested; and almost all of those for whom NHD lacks information on HCV test status will have tested HCV-antibody-negative.

Alternatively – **at the opposite extreme** - we might assume that the exposure-specific HCV-positive rates **when HCV-tested**, which we document in **Table B.3**, apply equally to those in the same exposure-group who, according to NHD, have not been HCV-tested.

Table B.4 therefore applies the above exposure-specific HCV-positive rates **when HCV-tested** to the persons with a bleeding disorder who shared the same exposure-route but were not HCV-tested according to the NHD.

Table B.4: Upper extreme for expected number who would test HCV-positive, together with 95% confidence interval (CI)

Well-defined subset: number not known at NHD as HCV-tested, see Table 3.1	Exposure to HCV at-risk products via				TOTALS
	Pre-1988 pooled plasma ONLY	Pre-1988 pooled plasma ONLY	Pre-1988 pooled plasma ONLY	EXPOSED to NEITHER**	
	477	658	438	9	1582
Upper extreme: expected number HCV-positive (95% CI)	66.6% of 477 = 318 (303 to 332)	15.2% of 658 = 100 (85 to 114)	81.4% of 438 = 357 (348 to 365)	9.8% of 9 = 0.9 (0.6 to 1.2)	776 Sum of variances = 134.4 (753 to 799)

** NEITHER patients may, however, have been exposed to pooled plasma during 1988-1991.

The resultant **upper extreme** is that 776/1582 (**49%**, 95% CI: 47.6% to 50.5%) of well-defined persons with a bleeding disorder who are not known to have been HCV-tested may, in fact, be HCV-antibody-positive (**95% CI: 753 to 799**), see **Table B.4**.

If this **upper extreme** estimate of 776 (49%) is closer to the mark than **zero** being HCV-infected among those in the **well-defined** cohort for whom the NHD has recorded their HCV-test-status as Not Known, then the HR in **Table A.1** for those whose HCV test status is **Not Known** should reflect that, after adjustment for demography and bleeding disorder/severity (for which exposure-route is a proxy), they are an almost equal mixture [49%; 51%] of those HCV-positive and those HCV-antibody-negative.

If the lower extreme applies, their associated HR would be as for those who had tested HCV antibody negative.

The estimated HR in **Table A.1** rules out the lower and suggests that the upper extreme of 49% is an over-estimation of the percentage who were truly HCV-infected, which is closer to 34% (or **540 persons**) according to **Table A.1**.

