FURTHER QUESTIONS ON STATISTICS

Dr CRM Hay's Response:

Patients with bleeding disorders – HCV

There is a discrepancy in the evidence before the Inquiry as to the number of patients with bleeding disorders likely to have been infected with HCV as a result of NHS treatment in Scotland.

The Scottish Haemophilia Directors estimated that 459 patients may have been infected with HCV as a result of treatment, albeit they considered that to be a "maximum" number or a "cautious overestimate".[1] Dr Tait considered that the minimum number was likely to be 314, on the basis that "314 represents the numbers that we know who are or have been Hepatitis C antibody positive, plus a small number who were never tested but we have evidence that they clinically suffered an episode of non-A non-B hepatitis".[2]

The UKHCDO estimated that 447 patients may have been so infected, albeit they considered that that was "probably an underestimate" since it did not include patients treated with blood or blood components (in particular, cryoprecipitate) rather than concentrates.[3]

The evidence from Health Protection Scotland was to the effect that that organisation was aware of 351 individuals in Scotland who have received blood factor, who have been diagnosed as HCV antibody positive and in respect of whom there was no information that they had received blood factor outside Scotland.[4]

Dr Tait and Dr Hay should each be asked the following questions: -

1. *What is the explanation for the discrepancy between these figures?*

There are three datasets, each compiled in a different way using different assumptions and with different strengths and weaknesses. Their relative merits and limitations are as follows: -

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[1] Methodology statement, [PEN.013.0016] at 0017, para 8
[2] Dr Tait, Day 14, Page 83 of the Inquiry Hearings Transcript and Methodology Statement, [PEN.013.0016] at 0017, para 8
[3] UKHCDO report, April 2012, page 51 and table 7, [PEN.019.0927] at 0983 and 0984
[4] Professor Goldberg, Day 6, Pages 116-119 of the Inquiry Hearings Transcript; see also statement of Professor Goldberg, [PEN.001.0206], question/answer 1

Professor Goldberg's Evidence:

This is based on actual anti-HCV tests on patients identified as having a bleeding disorder and/or treated with blood components or clotting factor concentrates. Health Protection Scotland are likely to underestimate the number infected for the following reasons:-

a) HCV antibody testing was introduced in 1991. Most of the patients reported from the HPS database were *first* tested in 1991-93 though some patients, presumably lost to follow-up for some time, were tested as late as the 2000s. Many patients who received concentrates likely to have transmitted HCV had died before they had the opportunity to be tested and some infected patients with infrequently treated mild bleeding disorders may still be lost to follow-up. We estimate that about a third of potentially infected patients will have escaped testing for these reasons.

b) Some patients may not have been identified as bleeders. The data on the HPS database is only as strong as the data provided to it. In the majority of cases, the type of bleeding disorder was not identified and HPS have no data on the type of product used. Further patients may have been tested but the relevant clinical details not presented so that they will not appear in this cohort, the link having not been made with blood component or blood-product usage.

c) HPS have no data on where the patient was infected, only where they were first tested. They may therefore include patients infected in England and now resident in Scotland but also include patients infected in England but now resident in Scotland It is difficult to know if this will lead to an over- or under-estimate or if the effect is broadly neutral in terms of total numbers.

d) A small number of patients will have been infected with HCV but resolved and will have lost their antibodies prior to testing. This is uncommon. I have only ever come across this twice and only once in my own practice.

Overall, I would estimate that these limitations are likely to lead Health Protection Scotland to underestimate the number of patients infected with HCV from treatment given for bleeding disorders by 25-30%.

Dr Tait's Evidence:

Dr Tait's figures are based, where available, on HCV test results and medical records cross-checked with UKHCDO Records. They are collated using different assumption to the UKHCDO data in that HCV testing is used where possible and it is assumed that HCV infection may have occurred from Plasma products rather than just from concentrate - there is published evidence for transmission of HCV by cryoprecipitate. This may affect the judgement about where (in Scotland or England) a patient was infected in the small number of patients who left Scotland prior to the widespread availability of concentrates. The strengths and weaknesses of these data are as follows: -

a) It is backed up by HCV testing in the majority of cases reported. Many patients will have died prior to the advent of HCV testing and their HCV status will therefore be unknown.

b) Most patients treated with Cryo in Scotland will have had severe haemophilia A and will have gone on to receive Scottish Concentrate and so although it may debated when they contracted their HCV infection (the first exposure to concentrate being the latest possible date) it is usually unarguable that they were infected from products administered in NHS Scotland.

c) Early records do not always exist. Either the patients have been lost to follow-up and the notes destroyed or they were managed outside a haemophilia centre by a district general hospital. As pointed out in the last report, a significant number of patients in the west of Scotland were managed outside a haemophilia centre until the early to mid nineteen eighties. Neither Glasgow nor UKHCDO will have any record of these patients prior to their management being adopted by the Glasgow Centre.

d) Where records existed but have now been destroyed, UKHCDO often has some record of treatment because we have retained everything submitted to us since 1969.

e) In some cases, records were found of some mild bleeders never reported to UKHCDO. Dr Tait highlights 15 of these (who were included in the updated UKHCDO report of April 2012). In our attempt to reconcile our data in early 2012, UKHCDO and the Scottish Directors did their best to fill any gaps in the

data and to reconcile the data to ensure that we were reporting on the *same list* of patients. There are inevitably gaps which we are unable to address.

By its nature, and given the previous attempt to reconcile the data, Dr Tait's report and the UKHCDO report largely coincide and share many of the same strengths, weaknesses and omissions. It is not surprising, therefore that the estimated number of infected patients is very similar in the two reports.

National Haemophilia Database Data:

The main assumption made when compiling the UKHCDO data is that patients would have been exposed to HCV *at the latest* when they were first exposed to concentrate. Concentrates were almost uniformly infectious for HCV during the period of risk. This risk diminished during 1985/6 when virally inactivated concentrates were introduced. Viral inactivation was successful in eradicating the risk of further HIV infection but the early products still transmitted HCV to some degree until 1986/7.

Many patients with severe haemophilia A or B will already have been infected from Cryo or plasma prior to their first exposure to concentrate, especially if very regularly treated. The risk of infection from blood components (FFP and single units of cryoprecipitate) was 0.5-1% per donor unit, prior to the advent of donor selection in the early eighties, falling by more than 90% even prior to the advent of universal HCV-antibody testing of blood donations in September 1991. Therefore, patients with severe haemophilia, who may have had hundreds of units of blood components prior to the advent of concentrate will, on the balance of probabilities have been infected with HCV from blood components and those with a mild and infrequently treated bleeding disorder will not, on the balance of probabilities have been infected.

In fact, data from the ongoing HCV-lookback exercise shows that 18.8% of those patients reported to have been treated with blood components only have evidence of exposure to HCV and 14% have active (HCVag +ve) infection.

When compiling the April 2012 report, we based our figures on known Concentrate exposure because we believed that this was solid data. For the years in question, we

had data on the type of blood product or blood component exposure but not the amount of each product used. This is not critical when assessing the HCV risk of concentrate, since a single dose was sufficient to transmit the infection in almost 100% of cases. For concentrate, the individual risk calculation would require detailed knowledge of the extent of exposure. For the group as a whole, however, an estimate can be made on the assumption that almost 19% of patients treated with blood components alone will have been infected with HCV.

Strengths and weaknesses of the data are as follows: -

Strengths: -

a) The data was collected contemporaneously rather than retrospectively and so the documentary evidence on which it was based was as complete as it was ever going to be. In some cases the original documentation has now been destroyed and so this is the only available evidence.
b) The data is compiled from data submitted by the managing centre.
c) We have data on patients who died before the advent of testing and data on patients subsequently lost to follow-up for which there is now no information available directly from the centres.

Weaknesses:-

a) The data is only as good as the submissions on which it is based. Some patients, almost exclusively those with milder bleeding disorders and especially those managed by district general hospitals rather than haemophilia centres have not been registered with the national Haemophilia Database and so we are unaware of them and have no data on them. The Scottish Directors and I have done our best to close at least some of these gaps, but I am sure that there will be other patients for whom neither NHD nor centres have any current information.
b) We do not believe that we have reliable data from many years ago on blood component therapy. That is why we adopted the conservative approach, basing our assumptions on Concentrate use and accepting that ours was an underestimate of the number of infected individuals. The additional data that we

have from the HCV lookback enables us to extend our estimate to include patients notified to us as having been treated with blood components only, however since 18.6% of this group were found to have evidence of exposure to HCV and 2/3rds of those had ongoing active infection.

c) A total of 86 patients have been reported to the database as having been treated with Blood components only (Red cells, plasma or cryoprecipitate). These were managed in Aberdeen (23pts); Dundee (4 pts), Edinburgh (18) patients, Glasgow (RI) (27 pts); Glasgow (RHSC) (11 pts) and Inverness (3 pts). Six of these also had treatment in England but only one was exclusively treated in England. This would yield an estimated further 16 patients infected with HCV in addition to those reported previously of whom about 10-12 would be expected to have chronic HCV. This estimate is, however based only on contemporary reports back to the database of treatment over the years. These reports may be incomplete, in which case this may still be an underestimate.

d) More accurate data may become available from the HCV lookback, when complete, but so far Scottish Centres have submitted only 20% of the data requested.

e) We have very limited HCV testing data. This does not prevent us from making firm assumptions about those treated with concentrate but may result in a misallocation of the infection to Scotland when the patient was infected from Cryo in England. This can, of course work both ways and may balance out. Furthermore, since the use of cryoprecipitate went largely out of use for Haemophilia in the early seventies, long before the advent of HCV ab testing, there can be no certainty one way or the other from which product most patients were infected.

Estimate of the number of patients exposed to hepatitis C, based on historical clotting factor concentrate exposure from a Scottish Haemophilia Centre		
Diagnosis	**Alive**	**Dead**
Haemophilia A	165	158
Haemophilia A with Liver Transplant	1	3
Acquired Haemophilia A	2	3
Haemophilia B	58	19
Females with VIII deficiency	7	0
Females with IX deficiency	4	0
von Willebrand disease	16	10
Temporary coagulation defect, now normal	1	0
	254	**193**

The table above was Table 7 in the April 2012 NHD Report to the Penrose Inquiry. It shows a diagnostic breakdown of patients thought to have been infected with Hepatitis C by virtue of exposure to Clotting factor concentrates during the period of risk.

Estimate of the number of patients exposed to hepatitis C, based on historical Plasma exposure from a Scottish Haemophilia Centre		
Description	**Alive**	**Dead**
Haemophilia A	18	9
Haemophilia B	1	2
Females with VIII deficiency	4	
Females with IX deficiency	3	
von Willebrand disease	33	6
F.VII deficiency	1	
F.XI Deficiency	1	
F.XII (Hageman) defect	1	
F.XIII Deficiency	1	
Fibrinogen Deficiency	1	
Platelet defects (misc)	2	
Unclassified	0	1
Temporary coagulation defect, now normal	1	
	67	**18**

This table shows a diagnostic breakdown of 86 Scottish patients exposed to blood components (plasma, cryoprecipitate and Blood or platelet concentrates) only and not exposed to concentrates during the period of risk. N.B. One patient with Haemophilia A, who is still alive, was treated exclusively in Colchester, although was registered at Glasgow R.I. As a result, he is excluded from the table above. Data from the HCV lookback exercise indicates that patients selected in this way will have a 19% probability of HCV infection. Whilst this approach permits me to estimate the proportion of this group exposed to HCV it does not permit me to identify individual patients likely to have been infected.

2. *Is one set of figures more likely to be correct and, if so, why?*

All three sets of figures are underestimates, even as currently amended. The reasons are outlined in 1. The amended UKHCDO figures are the closest the truth since they draw on the largest number of sources, have more complete representation of patients potentially at risk and are based almost exclusively on data collected contemporaneously.

3. *The Inquiry is aware that the UKHCDO is in the process of collecting data from haemophilia centres on Hepatitis C test results. Do the currently available results of that exercise allow for a more accurate estimate to be made of the number of patients with bleeding disorders in Scotland likely to have contracted HCV as a result of treatment?*

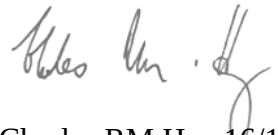
   Yes; see above in 1. It is necessary to extrapolate from the evidence available to produce an estimate, however, since the data from Scotland are still very incomplete.

4. *When is that exercise likely to be completed or, at least, reach a stage at which a more informed estimate can be made of the number of patients with bleeding disorders in Scotland likely to have contracted HCV as a result of treatment?*

   We aim to complete this exercise in 2013. It has proved far more difficult than anticipated and we have had to change our data collection instrument twice to make the data easier to collect.

5. *Has any further work been undertaken on the number of patients with bleeding disorders who were infected with HCV as a result of NHS treatment in Scotland who have died (including any further work in respect of the cause of death)?*

I don't think any more sophisticated work is possible though we are constantly updating the data as more patients die. The most up to date data is to be found in our current annual report, published in October of 2012, though this data is not broken down by country.



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