Variant Creutzfeldt-Jakob Disease (vCJD) in Blood and Blood Products

A statistical analysis of the probability of the occurrence and detection of vCJD in France over the last 20 years

Introduction

Since the UK Government banned the use of UK plasma for clinical use and for fractionation in 1998 for fear of transmitting variant Creutzfeldt-Jakob Disease (vCJD) from infected blood donors, 22 years have passed. During this period, the prevalence of this disease in the community has not materialised as first thought.

This disease stems from the consumption of contaminated beef put on the market from cows that had developed Bovine Spongiform Encephalopathy (BSE) when fed a mixture of cereals, meat and bone meal either made from BSE infected cattle or scrapie infected sheep offal. The BSE infection is attributed to a misfolded prion protein.

It is considered that as an infected animal is dressed in an abattoir its meat has a higher risk of contamination if it comes into contact with the brain, the spinal cord or the gastrointestinal tract which are known to contain higher levels of the infective prion.

This latter point may explain why so few people developed vCJD when significantly higher numbers of cows were found to have the disease. It is estimated that in the UK more than 184,000 cows were infected by BSE with the peak occurring in 1993 and just 2 cases reported in 2015.

In France, the government took the decision to continue to collect blood and use the plasma in clinical applications and in fractionation to produce the full range of blood products.

There has been a total of 178 deaths reported in the UK attributed to vCJD.

There has been a total of 27 deaths reported in France attributed to vCJD.

This paper explores, from a statistical perspective, the probability of detection of vCJD in recipients of blood and blood products in France over the last 20 years.

Method

To perform a statistical analysis of the probability of detection of vCJD in the recipients of plasma by transfusion and blood products from plasma fractionation several assumptions based on as many facts as possible must be established.

France has a population of 65, 291,847 people.

France has recorded 27 deaths attributed to vCJD.

The French government took the decision not to ban the use of plasma for direct clinical use or the indirect clinical use of blood products manufactured from plasma by fractionation.

The French Blood Transfusion Service collects 3,000,000 blood donations annually.

When the UK government decided to ban the use of UK plasma in 1998 there was a genuine concern within the UK Department of Health that blood plasma and blood products from a vCJD infected blood donor may transmit the disease. The French Government decided, after performing risk assessments, to inform patients of the benefit of plasma transfusions versus the risks. It is

considered that the risk is low, and the benefit is high from the continued use of plasma albeit the actual numbers of potentially infected blood donors could not be quantified.

If we assume that the annual incidence of vCJD is x cases for y blood donations used, what would be the probability of having observed 0 cases in 3,000,000 donations per year?

If this probability of detection is low, then one can be confident that the actual incidence of vCJD is most likely lower than the assumed incidence.

For example, if we imagine that the incidence is 3 cases per 1,000,000 blood donations then the probability of observing 0 cases in 3,000,000 would be about 0.01% which is extremely low. We can therefore be confident that the actual incidence is much less than 3 cases 1,000,000.

The Table below gives the Percentage Probability of observing Zero Cases per 3,000,000 donations based upon an assumed vCJD contamination rate per million:

Assumed vCJD Contamination Rate per million donations	% Probability of Observing 0 cases per 3 million donations
1 / 1 000 000	4,97869936873%
2 / 1 000 000	0,24787373042%
3 / 1 000 000	0,01234081381%
4 / 1 000 000	0,00061440649%
5 / 1 000 000	0,00003058908%
6 / 1 000 000	0,00000152292%
7 / 1 000 000	0,00000007582%
8 / 1 000 000	0,00000000377%
9 / 1 000 000	0,00000000019%
10 / 1 000 000	0,00000000001%

a. As the contamination rate per million increases so the percentage probability of observing zero cases per 3 million donations is much less likely. In other words, if there were 3 contaminated units per million donations then the probability of detecting them in a recipient would be 99.98766%. An extremely high likelihood of detection.
b. A reasonable hypothesis behind these calculations is that the 3,000,000 blood donations are used by different people. This allows for a good order of magnitude.

Impact of Time on the development of the disease.

Case 1 (“immediate” effect):

For example, we can say that each year for 20 years the annual vCJD contamination rate linked to blood donations is extremely low, very probably less than 3 cases per 1,000,000 donations.

If the disease really has an “immediate” effect, we could go even further by directly accumulating the 20 years of data, i.e. 0 cases out of 3,000,000 * 20 (60,000,000) blood donations used.

In this case, the previous table would become:

Assumed vCJD Contamination Rate per 10 million donations	% Probability of observing 0 cases per 60 million donations

1 / 10 000 000	0,24787514330%
2 / 10 000 000	0,00061442050%
3 / 10 000 000	0,00000152299%
4 / 10 000 000	0,00000000378%
5 / 10 000 000	0,00000000001%

a. Being able to accumulate years obviously gives more weight and confidence in the conclusion but does not really consider the possible time lag of the onset of the disease.
b. To clarify, if the blood donor pool contained 1 infected donation per 10 million donations then the probability of detecting this in a recipient of the combined total of 60 million donations is 99.75125%. An extremely high likelihood of detection.

Case 2 (“lagged” effect with 20 years of hindsight):

For example, we can say that the blood donations from 20 years ago indicate a vCJD contamination rate that is extremely low, very probably less than 3 cases per 1,000,000 donations. In this case we only use the first year, but we have 20 years of follow-up to check that the disease does not appear.

In this case, we therefore fully integrate the possible time lag of the disease, on the other hand the more recent data provide little or no information / confidence.

"The truth" is undoubtedly between these 2 configurations.

Example: 5 years of blood donations used then 15 years of minimum follow-up thereafter, we would have the following table:

Assumed vCJD Contamination Rate per 10 million donations	% Probability of observing 0 cases per 15 million donations used during 5 years with a minimum of 15 years follow-up.
2 / 10 000 000	4,97870534317%
3 / 10 000 000	1,11089890397%
4 / 10 000 000	0,24787492022%
5 / 10 000 000	0,05530833331%
6 / 10 000 000	0,01234094709%
7 / 10 000 000	0,00275363482%
8 / 10 000 000	0,00061441829%
9 / 10 000 000	0,00013709508%
10 / 10 000 000	0,00003059000%

a. To clarify, if the blood donor pool contained 2 infected donations per 10 million donations administered during a 5 year period followed by a 15 years follow-up then the probability of detecting these infected units in a recipient of the combined total of 15 million donations is 95.0213%. A high likelihood of detection.

Conclusion

From the statistical analysis of the continued clinical use of blood donations in France over the last 20 years it is clear that had vCJD been present in the blood donor population then there is an extremely high likelihood that infection would have been detected in recipients of blood and blood plasma ranging for example from: -

i. 99.98766% detection of the disease with an assumed rate of infection of 3 donors per one million donations
to
ii. 95.0213% detection with an assumed rate of infection of 2 donors per 10 million donations.

These results consider a rate of detection of infection from soon after administration up to 15 years of follow -up from 5 years after administration.

This statistical analysis therefore can conclude that the rate of infection of vCJD in the French blood donor population is vanishingly small if not non-existent.

The fact that no cases of vCJD have been seen from the continued clinical use of blood and blood products in France over the last 20 years bears out the decision to continue the use of a vital product whose benefits far outweigh any risks.

On this basis and with all the other information available since the ban on plasma was introduced 22 years ago, the UK government should now be in a strong position to reverse the ban and reintroduce the clinical use of this much valued resource.

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