Department of Health & Social Care

Risk assessment of the transmission of vCJD by blood components

Technical report

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Summary

This report considers the transmission of variant Creutzfeldt-Jakob Disease (vCJD) from person-to-person though receipt of donated blood components. It presents a mathematical model designed to examine how many future clinical cases and infections might be caused in this way. The model and its outputs have been reviewed by independent experts on the Advisory Committee on Dangerous Pathogens - Transmissible Spongiform Encephalopathies (ACDP TSE) Sub Group who support it as providing "both a highly precautionary estimate of the number of future cases and infections and also the only practicable way of assessing the benefit of further interventions until more empirical evidence becomes available".

The model assumes that there exists a large number of infected individuals in the UK population who are currently asymptomatic but could transmit their infection via the transfusion of blood components. To account for the scientific uncertainties about vCJD, it combines a scenario-based approach with Monte Carlo simulations. All input parameters for the scenarios modelled are sampled from agreed ranges with outputs rejected unless they are feasible when compared to the number of clinical cases observed to date. The model is highly precautionary so is likely to overestimate the number of future clinical cases and infections and may be subject to substantial change as understanding of the disease develops.

Despite the small number of clinical cases seen to date associated with blood transfusion, uncertainties in the current understanding of vCJD allow for a wide range of future estimates. However, compared with previous assessments the estimated risk is decreasing as more time passes since the last known case of blood-borne vCJD transmission and more is known about the disease.

The model gives the following estimates for the plausible number of vCJD cases associated with future infections: for red blood cells, from zero up to about 62 due to 90 million transfusions spread over the next 50 years; for plasma, from zero up to about 31 due to 14 million transfusions spread over the next 50 years; and for platelets, from zero up to about 84 due to 19 million transfusions spread over the next 60 years. These estimates that are supported by ACDP TSE Sub Group as being "of the right order of magnitude".

While the number of clinical cases due to future transfusions is low the number of asymptomatic vCJD infections could be much higher – though still small compared to those due to dietary exposure. The uncertainties in our basic understanding of vCJD present a fundamental difficulty in assessing the risk posed by blood-borne transmissions and make follow-up of “at risk” individuals and continued surveillance essential if evidence on vCJD risks is to accumulate.

Introduction

Variant Creutzfeldt–Jakob Disease (vCJD) is a fatal neurological disorder associated with the presence of an abnormal 'misfolded' form of prion protein (PrP). vCJD is currently untreatable and, once symptoms arise, leads to death within 18 months. It is believed that vCJD first spread to humans via dietary exposure to cattle infected with bovine spongiform encephalopathy (BSE) in the 1980s to early 1990s. Since 1996, stringent risk reduction measures have been in place to prevent further dietary exposure to BSE.

Clinical (symptomatic) cases of vCJD were first observed in the late 1990s and, despite most of the population being exposed to BSE, have remained relatively rare with only 178 observed in the UK to date (Details can be found on National CJD Research & Surveillance Unit website). There is evidence to suggest that around 1 in every 2,000 people in the UK might be carrying the abnormal PrP indicative of vCJD [Gill 2013]. Care must be taken, however, as vCJD, like other prion diseases, is believed to have an extremely long incubation period with clinical cases occurring decades after an individual was first infected. Not only might these infected individuals eventually develop into clinical cases but there is also the risk of secondary transmission especially via blood.

Of the 178 clinical cases, 175 are believed to be associated with dietary BSE exposure while the remaining 3 are associated with secondary transmission via the transfusion of blood. Even before these 3 cases were identified, Department of Health and Social Care (DHSC) policy was based on the presumption that vCJD is transmissible from person-to-person via the transfusion of blood. This led to the introduction of several risk reduction measures: the importation of fractionated plasma derivatives (1999); leucodepletion (1999); the importation of fresh frozen plasma for children and certain groups (recipients born on or after 1st January 1996 in 2004 and those suffering from thrombotic thrombocytopenic purpura in 2006); excluding recipients of blood components and products since 1980 from donating (2004); and the use of apheresis platelets in recipients born on or after 1st January 1996 (2005).

To ensure that risk reduction measures are proportionate and represent value for money to the UK health system, risk assessments have been performed by DHSC to model the number of future infections and clinical cases of blood-borne vCJD in the UK. This report covers the most recent update to the DHSC model and includes the risk reduction measures that were in place in August 2018. Details of the risk assessment in support of the decision announced in September 2019 on the use of imported plasma and apheresis platelets for recipients born on or after 1st January 1996 can be found in the Risk reduction measures for variant Creutzfeldt-Jakob disease: PCWG report.

As there is still a lot of uncertainty in the current scientific understanding of vCJD, the modelling takes a highly precautionary approach, so is more likely to over- than underestimate the number of future infections and cases, and produces estimates with a wide range of possible values. The latest model was presented to the independent experts on the Advisory Committee on Dangerous Pathogens - Transmissible Spongiform Encephalopathies (ACDP TSE) Sub Group who issued the following statement in September 2018:

> "The revised model was considered by the ACDP TSE Sub Group at its meetings of 8th February 2018 and, following further specific correspondence between the author and certain committee members who recommended changes, was re-circulated by email to members in August 2018. The committee were happy to support it as providing both a highly precautionary estimate of the number of future cases and infections and also the only practicable way of assessing the benefit of further interventions until more empirical evidence becomes available. Specific figures for the number of cases and infections, while uncertain and subject to revision in the light of further data, are considered to be of the right order of magnitude."

Background

Blood components

Blood is composed of four main *components* that generally serve different functions in the body: plasma, red blood cells (RBC), white blood cells, and platelets. When an individual goes to donate blood, it is collected in one of two ways: either as whole blood taken directly from a vein which is then separated into its individual component parts; or via a process called apheresis in which the donor's blood passes through a filter which extracts mainly platelets. These raw components are then further processed into different units that can be transfused separately dependent on patient need. For each unit transfused, the recipient will be exposed to a substantial volume of material from one (or even several) donors.

Plasma can also be further processed into fractionated plasma *products*, such as Factor-VIII used to treat haemophilia, by "fractionating" pools of many thousands of donations. For each product, recipients are exposed to tiny amounts of material sourced from a large number of donors. Since 1999, plasma for fractionation has been imported as a vCJD risk reduction measure.

While blood donations can be used for blood components and/or fractionated plasma products, the DHSC model only considers the most commonly used blood components, specifically RBCs, platelets (from whole blood and apheresis), and plasma.

Clinical cases of vCJD

To date, there have been 178 definite or probable vCJD cases in the UK (Definite, probable and possible cases are classified according to specific criteria developed for epidemiological studies of prion disease agreed by the World Health Organisation. Details can be found on National CJD Research & Surveillance Unit website). 175 of these cases are believed to be associated with dietary BSE exposure and the remaining 3 associated with secondary transmission via RBC transfusion. Preclinical (asymptomatic) vCJD has also been observed in two individuals who died of other causes: one attributed to an RBC transfusion and the other to fractionated plasma products.

As with other prion diseases, vCJD is believed to have an extremely long incubation period with clinical cases occurring decades after an individual was originally infected. All observed transmissions have been due to RBC transfusions that occurred prior to the introduction of leucodepletion in 1999 (the removal of white cells thought to contain most of the infectious agent that causes vCJD) yet the last known clinical case occurred in

2006. No transmissions have been observed due to transfusions of plasma or platelet components.

The development of vCJD is influenced by the genetic factors of the infected individual. In particular, differences at position (codon) 129 of the individual's PrP gene. These differences can take one of three forms: About 40% of the UK population have the methionine amino-acid at this position (MM homozygote); 10% have the valine amino-acid at this position (VV homozygote); and the remaining 50% have both methionine and valine amino-acids (MV heterozygote). Of the 178 definite or probable vCJD cases 161 have been genetically tested: 160 were methionine homozygous (MM) at codon 129 of the PRNP gene; while only 1, the most recent case reported in 2016 associated with dietary exposure, was methionine-valine heterozygous at codon 129 (MV). Of the two preclinical vCJD cases both were MV heterozygous at codon 129. To date no cases have been found in valine homozygotes (VV). There is a biochemical reason why prion disease will generally be more common in either VV or MM homozygotes, compared with MV heterozygotes, as the crystal-like deposition of the protein is less likely where there are different isoforms present. For any particular prion there may be a predilection to one isoform or the other and MVs will always have a modest (and difficult to quantify) degree of protection.

Previous modelling

The underlying methodology used in this model was originally published in the previous DHSC risk assessment carried out in 2013. The version of the modelling presented here has been revised in several key areas based on the latest advice of ACDP TSE Sub Group:

- the input parameter and calibration ranges have been updated to account for the lack of any further known clinical cases of vCJD attributable to transfusion;
- the calibration process has been altered to allow for the possibility of greater under-ascertainment of clinical cases in the elderly;
- the distribution of dietary exposure has been modified to incorporate ACDP TSE Sub Group’s more precautionary interpretation of the Appendix III prevalence study (see below);
- new unit types have now been explicitly included in the model, specifically cryoprecipitate in the plasma model and pooled platelets in PAS in the platelet model;
- the relative infectivity of platelets and the impact of leucodepletion on secondary transmission via plasma and platelet components has been updated to reflect the results of ovine experiments.

In the 2013 model, it was assumed that the majority of vCJD infectivity was associated with plasma as this was supported by rodent experiments. Recently, there has been a growing body of literature that suggests that determining the level of infectivity of blood components by intracranial inoculation of rodents does not accurately predict their ability to transmit when administered intravenously. As such, the latest model relies on results from ovine experiments as these seems to represent a better model for humans.

Modelling

Overview

To estimate the number of clinical cases and infections of vCJD due to secondary transmission by blood transfusion, an analytical probabilistic model was developed by DHSC in conjunction with Clinical Operational Research Unit (CORU) University College London. This is a conceptually simple model that combines population data for both blood donors and recipients with probability distributions describing various aspects of the disease to calculate expected values (the probability-weighted average of all possible outcome values) for the number of clinical cases and infections.

The base modelling assumes that the UK population was infected with vCJD due to dietary exposure to BSE. Following infection, there will be some delay prior to the onset of infectivity in an individual's blood. If these now infectious individuals go on to donate blood, there is a chance that any units derived from their infective donation will themselves be infective. When recipients of blood transfusions are given such an infective unit they will become infected with vCJD and may go on to develop clinical symptoms at some later date.

The risk assessment comprises three separate versions of the model covering each of the main blood component types:

- Red blood cell (RBC), with RBC units produced from individual whole blood donations.
- Plasma, which includes: Fresh frozen plasma (FFP) units produced from individual whole blood donations; cryoprecipitate (single) units produced from individual whole blood donations; and cryoprecipitate (pooled) units produced from pools of 5 whole blood donations.
- Platelet, which includes: Apheresis platelet units, produced from individual apheresis donations; pooled platelets in plasma, produced from pools of 4 whole blood donations; and pooled platelets in platelet additive solution (PAS), produced from pools of 4 whole blood donations. These replaced pooled platelets in plasma from mid-July 2015.

For each of the component models the input parameters are the same and the mathematical structure and calibration ranges are broadly similar with any differences highlighted in this report.

Following a precautionary principal, it is assumed that infected individuals may remain asymptomatic but are still able to transmit the infection through donated blood and so act

as subclinical carriers. This would mean that a large reservoir of latent infectivity might potentially exist in the UK blood donor population which could then be transmitted via the transfusion of blood components and lead to the development of clinical cases of vCJD in blood recipients. If there is no such carrier state and instead only individuals who go on to develop clinical symptoms of vCJD can transmit the disease then it is highly likely that the number of future clinical cases and infections will be far lower than estimated by the model.

As development of vCJD is influenced by genetic factors, with all but one of the clinical cases to date in codon 129 MM homozygotes, the modelled donor and recipient populations are split into MM homozygote (40%) and non-MM homozygote (60%) groups based on the prevalence of these genotypes in the UK population. For each of these genotype group different model parameters are used. This is a precautionary assumption as it means that both MV and VV individuals are equivalent in terms of their infectivity, susceptibility to clinical symptoms, and incubation periods which is unlikely to be the case (see above). Recipients of transfusions are further split into acute or chronic groups to account for differing transfusion patterns and survival probabilities.

The model makes the precautionary assumption that all recipients of an infective unit will be infected, though may not go on to develop symptoms i.e. all recipients are completely susceptible to infection. To account for the relatively small number of clinical cases observed to date and their relatively rapid onsets two possible epidemiological scenarios are modelled: A *rapid onset* MM homozygote subgroup, in which a variably sized subset of the MM population exhibits rapid onset of clinical symptoms; and a *variable clinical attack rate* (CAR) scenario, in which the susceptibility to developing clinical vCJD can vary and is independent of the recipient's genotype. Further details on each of these are given later.

Due to the limited evidence and scientific uncertainties around vCJD, the model uses a Monte Carlo simulation to sample the input parameters and generate a collection of possible distributions for the number of clinical cases of blood-borne vCJD. For each model run in the simulation, it first samples from the specified ranges across all input parameters and then rejects them unless the resulting number of clinical cases calculated matches what has been observed (including some flexibility to account for possible case under-ascertainment). This allows us to incorporate uncertainty into our estimates while ensuring that the model outputs are feasible via this calibration process. The input parameter and calibration ranges used in the model were agreed by experts on ACDP TSE Sub Group on 8th February 2018.

Current vCJD risk reduction measures

There are several vCJD risk reduction measures in place as of 2019 that need to be considered in the modelling:

- importation of fractionated plasma derivatives (1999) – as the model is only concerned with infections associated with the transfusion of blood components this is not included.

- leucodepletion of blood components (1999) – all component models explicitly include a decrease in the transmission probability (the probability that a unit from an infectious donor will be infective) following the introduction of leucodepletion.

- importation of plasma for under 16s and those born on or after 1st January 1996 (2004) – the model assumes that there is no risk of vCJD from imported plasma. The decrease in the number of recipients of UK sourced plasma for each year modelled has been calculated by using the proportion of recipients born on or after 1st January 1996 given by the 2016 mid-year population estimates from the Office of National Statistics (ONS).

- excluding recipients of blood components and products since 1980 from donating (2004) – this policy was intended to stop any possible further transmissions via blood. As the number of blood recipients is small compared to the UK population the model does not explicitly include any impact from this policy.

- use of apheresis platelets in recipients born on or after 1st January 1996 (2005) – transfusing apheresis (taken from a single donor) rather than pooled platelets reduces the number of donors a recipient is exposed to and so potentially reduces any vCJD risk. This policy is captured by the varying proportion of apheresis units used over time (see below). The model assumes that apheresis platelets are preferentially transfused to younger patients with other recipients receiving pooled platelets.

- importation of plasma for individuals suffering from thrombotic thrombocytopenic purpura (TTP) (2006) – the model assumes that TTP recipients receive around 3% of all plasma units per year (based on data from Scottish National Blood Transfusion Service (SNBTS)) and that these units are imported so have no risk of vCJD.

Inputs

Prevalence of infected individuals in the donor population

Immunohistochemical (IHC) staining studies have demonstrated the presence of disease-related PrP in lymphoreticular and other tissues, with samples classed as positive showing similar patterns of staining to those found in clinical cases of vCJD. While it is unclear if such positive staining necessarily indicates that blood from an individual would be infective, the precautionary assumption is made that any individual whose tissues stain positive are subclinical carriers who are infected with vCJD and so have the potential to transmit this infection via their blood.

To investigate the number of subclinical carriers in the UK population, various studies have tested for the presence of disease-related PrP in stored tissue samples. These concentrated largely on the population born between 1961 and 1985 as this cohort is known to have been exposed to significant levels of BSE. The largest of the studies (known as the Appendix II study) tested 32,441 appendix samples, of which 16 were positive [Gill 2013]. This was interpreted as meaning that around 1 in 2,000 of the UK population may be infected with vCJD and potentially could transmit this infection via donated blood.

A further appendix study (known as Appendix III) was carried out to investigate the hypothesis that there would be an absence of positives in appendices removed prior to 1980 and in those taken from individuals born after 1st January 1996 as these cohorts were not exposed to significant levels of BSE (results reported in Health Protection Report volume 10 issue 26). Unexpectedly, small numbers of positives were found in both cohorts though none were from appendices *removed before 1978* or from patients *born after 2000*. While the precise meaning of these positives is unclear, the DHSC model takes the more precautionary interpretation of the results given in the ACDP TSE Sub Group's August 2016 'Updated position statement on occurrence of vCJD and prevalence of infection in the UK':

> "…while there is no statistical difference in prevalence of vCJD -related abnormal prion protein across birth and exposure cohorts, the central estimates vary in a direction consistent with the changing intensity over time of the observed BSE epidemic in cattle. All may therefore be attributable to BSE exposure. However, this conclusion suggests that human exposure began in the late 1970s and continued through the late 1990s, albeit at a lower rate than in the mid-1980s."

To model this interpretation the annual incidence of vCJD infection (individuals exposed to dietary BSE who would have potentially infective blood) is assumed to follow a truncated normal distribution with a mean of 1989 (corresponding to the peak in dietary BSE exposure that occurred prior to the specified bovine offal ban) and a variable standard deviation. The annual incidence is truncated to 0 before 1978 and after 2000, to account for the lack of positives in these times periods, and then scaled so that the annual incidence from 1978 to 2000 sums to the maximum observed prevalence of 1 in 1,800, corresponding to that in the maximally exposed age group in the Appendix II study (11 positives in 20,117 samples). As the Appendix II study found the positive appendix samples were distributed across all codon 129 genotypes, the same incidence is used in modelling both MM and non-MM homozygote donor groups.

To account for the uncertainty in the scale and timing of BSE exposure, random sampling of the distribution's parameters is performed for each Monte Carlo model run. The standard deviation (defined prior to truncation) of the truncated normal distribution is

uniformly sampled from the range 3.5 to 10 years, corresponding to an annual incidence in 1978 (and also by symmetry 2000) of between 1% and 50% of the peak incidence in 1989. The maximum prevalence used to scale the distribution is then sampled from the range 1 in 1,000 to 1 in 3,700, representing the 95% credible interval of the observed positives, using a gamma distribution. These ranges were agreed by ACDP TSE Sub Group.

Using the Appendix II study results as a measure of prevalence is predicated on the following assumptions: the likelihood of having your appendix removed is independent of the presence of disease-related PrP in lymphoreticular and other tissues; enough time has elapsed between initial infection, due to dietary exposure to BSE, and the accumulation of signal in the individuals' appendix tissue at the time of removal to stain positive; and that the appendix samples themselves come from a representative sampling of the general population.

Onset of vCJD infectivity in infected donors

If an individual were to become infected with vCJD due to dietary exposure to BSE it is unlikely that their blood would become infectious immediately. The known secondary RBC-borne transmissions of vCJD involved donations taken between 17 and 42 months prior to the onset of symptoms in the donor (see the Transfusion Medicine Epidemiology Review (TMER) website for details). As the incubation period for vCJD following dietary exposure is thought to be around 10 years, this implies infected individual's blood can be infectious at around two thirds of the way (65%) through the incubation period. However, ovine transfusion experiments [McCutcheon 2011] show that blood taken no more than 25% through the donor animal's incubation period can infect.

For modelling purposes, the proportion of infected donors whose blood has become infective is modelled in all components using a cumulative normal distribution with a mean and standard deviation dependent on genotype. To account for the uncertainty in the onset of infectivity, the ACDP TSE Sub Group agreed a mean and standard deviation for each genotype in the range 1 to 19 years and 0 to 10 years respectively which are uniformly sampled for each Monte Carlo model run. The resulting cumulative normal distributions are then multiplied with the annual incidence of dietary exposure to vCJD in previous years and summed to give the proportion of the general population of a particular genotype who would have infective blood in any given year.

Infectivity of blood components from infectious donors

There have been 67 recipients of blood components from donors who went on to develop vCJD. So far, 8 of these recipients have been tested and only 4 showed evidence of vCJD transmission (see the Transfusion Medicine Epidemiology Review (TMER) website for details). Given the high level of uncertainty and relatively small number of clinical cases of vCJD seen to date, the ACDP TSE Sub Group agreed the maximum possible range for the

transmission probability (the probability that a unit will be infective) of 0% to 100% per unit of non-leucodepleted RBCs transfused from an infectious donor. While this range allows for very low transmission probabilities the calibration process ensures the model is still highly precautionary. For the other blood components, experiments conducted at the Roslin Institute [McCutcheon 2011] using an orally infected BSE sheep model of blood transfusion demonstrated that the transmission probability for platelets and plasma derived from whole blood was of a similar order to that of RBCs. As such the ACDP TSE Sub Group agreed using the same range of transmission probabilities as for RBCs in the platelet and plasma component models.

The impact of leucodepletion on infectivity is also unclear. While animal models demonstrate vCJD transmission from leucodepleted blood components the lack of clinical cases in humans following the introduction of leucodepletion implies a significant effect. To account for this uncertainty, the ACDP TSE Sub Group agreed a transmission probability that was both lower than for non-leucodepleted RBCs and in the range of 0% to 20% per unit of leucodepleted RBCs from an infectious donor.

Further data provided by the Roslin Institute on their sheep model (unpublished data) supports the belief that, considering only paired leucodepleted and non-leucodepleted units transfused from the same BSE-infected donor, the probability of transmission appears reduced in plasma, platelet, and RBC components following leucodepletion. While these experiments are not sufficiently powered to make a quantitative comparison and are based on units that do not exactly match those included in the DHSC model, ACDP TSE Sub Group agreed using the same ranges of transmission probabilities for RBCs (both leucodepletion and non-leucodepleted) in the platelet and plasma component models. All transmission probabilities are uniformly sampled for each Monte Carlo model run.

Susceptibility and incubation following secondary transmission

There is relatively little data on the susceptibility to infection of an individual who receives an infective unit or the incubation period prior to the onset of clinical symptoms following secondary transmission by blood. Of the three known cases of clinical vCJD transmitted via RBCs incubation times varied between 6.5 and 8.3 years. In contrast, there are still (as of June 2018) living individuals who received blood from donors who went on the develop vCJD who have no symptoms after 15 years (see the Transfusion Medicine Epidemiology Review (TMER) website for further details). The model makes the precautionary assumptions that: All recipients regardless of genotype are completely susceptible to infection (though this infection may be subclinical); and that the incubation period due to secondary transmission, which is genotype dependent, can be modelled using a gamma distribution to allow for the potential of long incubation periods as seen in other prion diseases. ACDP TSE Sub Group agreed a range for the mean incubation following secondary transmission of 1 to 20 years for MM homozygote and 20 to 40 years for non-

MM homozygote recipient groups that are uniformly sampled for each Monte Carlo model run.

To account for the relatively small number of blood-borne clinical cases of vCJD observed to date and their relatively rapid onsets two possible epidemiological scenarios are modelled:

- A *variable clinical attack rate* (CAR), in which the susceptibility to developing clinical vCJD is varied and is genotype independent. For each Monte Carlo model run, the probability that an infected individual develops clinical vCJD is uniformly sampled from the range 0% to 100% ACDP TSE Sub Group agreed with this scenario and have stated that the clinical susceptibility in the non-MM genotype group would likely be less than that in the MM genotype group and so using the same susceptibility across all genotypes represents a precautionary assumption.

- A *rapid onset* MM homozygote subgroup, in which all individuals infected with vCJD will develop into clinical cases but there exists a subset of the MM population exhibiting rapid onset of clinical symptoms. This is done by introducing an additional rapid onset MM genotype group into the component models with its own parameters for the onset of infectivity after dietary infection (same range for mean and standard deviation) and a shorter incubation time following secondary transmission than the other genotypes (range 1 to 20 years). ACDP TSE Sub Group agreed that the proportion of the population (donor and recipients) in this group should be uniformly sampled from the range 0% to 15% for each Monte Carlo model run. The size of the "normal" MM genotype group is then scaled to ensure MM genotypes in total make up 40% of the population and the mean incubation following secondary transmission for this group sampled from an expanded range of 1 to 40 years.

The variable CAR scenario is functionally equivalent to one in which the relatively small number of blood-borne clinical cases observed is due to different strains of infective agent, e.g. either “lymph-seeking” or “brain-seeking”. As such, no further scenario to model this possibility is performed.

Donors

The historical distribution of whole blood and apheresis platelet donors by age (Appendix 1: Table 5) was based on studies carried out by the UK Blood Services and is assumed to remain constant across the modelled period. It is further assumed that the prevalence of individuals infected with vCJD and the proportion of MM and non-MM homozygotes in the donor population is the same as that in the general population.

As the majority of whole blood donors stop donating by the age of 70 and individuals born after 2000 are assumed not to have had dietary exposure to vCJD, the RBC and plasma

component models assume there are no new vCJD infections after 2070. As apheresis donors can be older with the majority stopping by the age of 80, the platelet component model assumes there are no new vCJD infections after 2080. While there are no new infections, there may still be clinical cases after these dates due to previous transmissions.

Recipients

For modelling purposes, recipients of blood are split into two groups: *acute* recipients who undergo blood transfusions as part of a one-off treatment with an associated survival probability and, given they survive, are assumed to have a life expectancy comparable to the general population (taken from ONS 2014 - 2016 National Life Tables); and *chronic* recipients who receive regular transfusions over an extended period of time and are assumed to have a decreased life expectancy compared to the general population.

Data on the number of units received by age group was taken from: 2014 National Red Cell Survey for RBCs; 2009 Audit of the use of Fresh Frozen Plasma for FFP; and 2001 EASTR study (see [Wells 2009]) for platelets. As only total usage was available, the data on platelets and FFP was then combined with 2013 - 2018 patterns of usage provided by the Scottish National Blood Transfusion Service (SNBTS) to determine the proportion of acute and chronic recipients of plasma (including cryoprecipitate) and platelets by age group. The distribution of units by recipient age group and type can be seen in Appendix 1: Table 6, Table 7, and Table 8 for RBC, plasma, and platelets respectively. The precautionary assumption is made that each unit is transfused to a different recipient as this maximises the size of the recipient population and so will increase the estimated number of clinical cases.

The reduced life expectancy of blood recipients has been modelled by fitting the average survival probability of acute recipients and the average life expectancy of chronic recipients . These values are altered so that the average life expectancy in all recipients matches the 1, 5, and 10 year survival rates obtained from the EASTR study [Morley 2016]. For all recipients, life expectancy is limited to 100 years old.

As annual blood usage data is not available, data on the total number of units issued between 2000 and 2017 was taken from Serious Hazards of Transfusion annual reports for the whole of the UK. For the modelled period prior to 2000 and after 2017 the number of units issued is held flat at these values. Using issues data for the number of units transfused is precautionary as it does not account for any wastage and so maximises the number of recipients. The issues data used in the modelling can be seen in Appendix 1: Table 9.

For the plasma model, units of FFP, cryoprecipitate (single), and cryoprecipitate (pooled) are combined by converting to single unit equivalents (based on cryoprecipitate pools derived from 5 whole blood donations). This relies on the assumption that the infectivity in

FFP and cryoprecipitate is the same which has been agreed by ACDP TSE Sub Group. The number of issues are then adjusted to account for the reduction in the use of UK sourced plasma each year due to the importation of plasma for under 16s, those born on or after 1st January 1996, and individuals suffering from TTP (see above).

For the platelet model, pooled units in plasma and pooled units in PAS are combined (as they both have the same number of donor exposures and were used concurrently) and apheresis units considered separately. The annual number of apheresis platelets issued was calculated by assuming that for each year the proportion of all platelets issued in the UK that are apheresis units was the same as the proportion issued by England's NHS Blood and Transplant (NHSBT) (data provided by NHSBT).

In total the model assumes: around 200 million red blood cell transfusions will occur between 1978 and 2070 with 90 million occurring from the end of 2019; around 33 million UK sourced plasma transfusions (single unit equivalent) will occur between 1978 and 2070 with 14 million occurring from the end of 2019; and around 31 million platelet transfusions (of which approximately 50% are apheresis) will occur between 1978 and 2080 with 19 million occurring from the end of 2019.

Formulation

The analytical blood component model can be broken down into three stages: (i) the distribution of blood donors who, at any point in time, will have infectious blood; (ii) the probability that an individual who receives a unit from an infectious donor will become infected; and (iii) the distribution of infected recipient who go on to develop clinical symptoms of vCJD.

The model is specified in discrete annual intervals indexed by $t = t\_0, t\_0 + 1, t\_0 + 2, \ldots, t\_N$, where $t\_0 = 1978$ corresponds to the start of dietary exposure to BSE and $t\_N = 2120$ the date by which all clinical cases are expected to have occurred. Throughout, all blood donors and recipients are separated into cohorts based on their codon 129 genotype group (groups are either MM and non-MM for the variable clinical attack rate scenario or rapid onset MM, MM, and non-MM for the rapid onset scenario) indexed by g.

Infectious donors

The annual incidence of vCJD infection due to dietary exposure to BSE in the donor population is modelled using a discrete normalised truncated normal distribution, Φ, centred on 1989 and given by:

$$E[t] = E_T * \Phi\left[\frac{t - 1989}{\sigma_E}\right]$$

where E_T is the maximum prevalence determined by the results of the Appendix II study, σ_E is the standard deviation of the normal distribution prior to truncation, and the sum of Φ is normalised to 1 with the properties $\Phi[t < 1978] = \Phi[t > 2000] = 0$.

We assume that the time gap between initial dietary infection and the point where an infected individual's blood becomes infectious can be approximated by a normal distribution, with mean delay μ_g and standard deviation σ_g dependent on the individual's genotype group. The prevalence of people with infectious blood in the donor population aged a is then:

$$V_a[t] = \sum_g \sum_{\tau=0}^{a} \pi_g * E[t-\tau] * F_\Phi\left(\frac{\tau - \mu_g}{\sigma_g}\right)$$

where π_g denotes the proportion of the donor population who are in genotype group g, and F_Φ is the cumulative normal distribution. This assumes that the prevalence of vCJD infection across all genotype groups is the same.

Members of the donor population are separated into age cohorts indexed by $a = a\_0, a\_0 + 1, a\_0 + 2, \ldots, a\_N$, where $a\_0 = 16$ is the youngest age and $a\_N = 80$ the oldest, corresponding to the ages at which individuals can donate blood. The proportion of all blood donated in year t that is from infectious donors is then given by:

$$I[t] = \sum_a D_a * V_a[t]$$

where D_a denotes the proportion of donors who are aged a.

Infected recipients

The transmission probability (the probability that a unit from an infectious donor will be infective) associated with the transfusion of a single unit of the particular component type is separated into two periods, to account for any impact of leucodepletion, over which the probability is assumed to be constant. Leucodepletion of blood components was first introduced in 1998 and is believed to have an effect on the transmissivity of vCJD. To account for this, a modified Heaviside step function is used such that the transmission probability is given by:

$$\beta[t] = \begin{cases} \beta_0, & t < 1999 \\ \beta_1, & t \geq 1999 \end{cases}$$

where β_0 is the transmission probability of vCJD without leucodepletion and β_1 is the transmission probability following leucodepletion and has the property $\beta\_1 \leq \beta\_0$.

Letting M denote the number of donor exposures per unit, i.e. the number of donated issues used to make the unit, then the probability per unit transfused that an individual becomes infected with vCJD in year t is given by:

$$P_M[t] = 1 - (1 - \beta[t] * I[t])^M$$

The number of infections in year *t* for each unit type is then given by multiplying this probability with the number of units issued in that year.

This formulation assumes that the transfused units are independent of one another and that the distribution of potentially infective units is uniform across the blood supply. We further assume that once an individual has been infected any further infection has no effect and that the size of the recipient population is not significantly changed by the loss of infected individuals.

Development of clinical cases

Following infection, we assume that individuals can have a variable susceptibility to developing clinical vCJD, *ω*, independent of their genotype group corresponding to a variable clinical attack rate. In these symptomatic individuals, the incubation period prior to the onset of clinical symptoms is parameterised using a gamma distribution with genotype group dependent mean *Δ_g* and group independent shape *κ*. The probability of onset of clinical vCJD *τ* years after infection (assuming the patient has survived), for an individual of genotype group *g*, is then:

$$O[\tau, g] = \omega * \Gamma\left[\tau; \kappa, \Delta_g/\kappa\right]$$

where *Γ[τ; κ, θ]* is the discrete normalised gamma probability density function (normalised to 1), with shape parameter *κ* and scale parameter *θ.*

For each unit type in the blood component model, the number of clinical cases of vCJD in year *t* can then be modelled as:

$$Q_M[t] = \sum_{\tau=0}^{t-t_0} \sum_{g} N_M[t-\tau, \tau] * \pi_g * O[\tau, g] * P_M[t-\tau]$$

where *N_M[t, y]* is the number of units transfused in year *t* to individuals who have survived for *y* years and is given by:

$$N_M[t, y] = T_M[t] * \sum_{\alpha} R_C[t, \alpha, M] * \exp\left(-\frac{y}{\lambda_C}\right) + S * R_A[t, \alpha, M] * \exp\left(-\frac{y}{\lambda_\alpha}\right)$$

where *T_M* is the total number of units issued in year *t*, *R_C* and *R_A* are the proportion of all recipients of those units in age group *α* who are chronic and acute respectively, *S* is the fitted average probability of acute recipients surviving the clinical event, *λ_α* is the mean life-expectancy of age group *α* in the general population, and *λ_C* is the fitted mean life-expectancy of chronic recipients of that blood component. Life expectancy is limited to 100 years of age.

The total number of clinical cases of vCJD for each blood component model is then given by the summation of the number of cases due to each unit type (and similarly for the number of infections).

Parameterisation

The inputs of the blood component model are split into two sets corresponding to the two epidemiological scenarios: *variable clinical attack rate* and *rapid onset* (see Table 1). All input parameter ranges are sampled using uniform distributions as part of the Monte Carlo simulation with the exception of the maximum prevalence of infected donors which is sampled using a gamma distribution. Two additional constraints are applied to the sampling: the transmission probability following leucodepletion must always be lower than that before leucodepletion; and the mean incubation period following secondary transmission (secondary incubation period) of the rapid onset MM subgroup must be less than for the MM subgroup.

Table 1 Input parameter ranges for variable clinical attack rate (CAR) and rapid onset scenarios sampled by the Monte Carlo simulation.

Input parameter	Variable CAR scenario	Rapid onset scenario
Maximum prevalence of infected donors	547 per million (range 273 – 978)	547 per million (range 273 – 978)
Standard deviation of prevalence of infected donors	3.5 – 10 years	3.5 – 10 years
Onset of infectivity after dietary infection: rapid onset MM	N/A	1 – 19 years (SD 0 – 10 years)
Onset of infectivity after dietary infection: MM	1 – 19 years (SD 0 – 10 years)	1 – 19 years (SD 0 – 10 years)
Onset of infectivity after dietary infection: non-MM	1 – 19 years (SD 0 – 10 years)	1 – 19 years (SD 0 – 10 years)
Transmission probability per exposure: non-leucodepleted	0% – 100%	0% – 100%
Transmission probability per exposure: leucodepleted	0% – 20%	0% – 20%
Mean secondary incubation period: rapid onset MM	N/A	1 – 20 years
Mean secondary incubation period: MM	1 – 20 years	1 – 40 years

Input parameter	Variable CAR scenario	Rapid onset scenario
Mean secondary incubation period: non-MM	20 – 40 years	20 – 40 years
Secondary incubation period: shape parameter	1	1
% population MM rapid onset	N/A	0% – 15%
Clinical attack rate (CAR)	0% – 100%	100%

Calibration

To ensure that the outputs produced by each Monte Carlo model run are feasible they are rejected unless the estimated number of clinical cases of vCJD falls within a specified calibration range dependent on component type. To account for the possibility of a higher level of under-ascertainment of vCJD in the older population the models are calibrated against clinical cases in recipients aged 75 years or younger (as this corresponds to the age group in which all three clinical cases due to RBC-borne transmission were identified). Calibrating in this way is highly precautionary as it means that there is no limit on the number of clinical cases modelled that occur in recipients over the age of 75. These calibration ranges for recipients aged 75 years or younger have been agreed by ACDP TSE Sub Group.

Red blood cell model calibration range

Between 1989 and 2011 inclusive:

- A maximum of 10 RBC-borne clinical cases of vCJD in recipients under the age of 76 in any genotype group;
- A minimum of 3 RBC-borne clinical cases of vCJD occurring in MM homozygotes under the age of 76 due to non-leucodepleted RBCs and with onset between 2002 and 2006 inclusive, corresponding to the diagnosed cases;
- Of the 7 potential un- or misdiagnosed RBC-borne clinical cases of vCJD a maximum of 3 occurring in non-MM homozygotes under the age of 76.

Between 2012 and 2016 inclusive:

- A maximum of 3 RBC-borne clinical cases of vCJD in any genotype group in recipients under the age of 76 that have been un- or misdiagnosed.

Plasma model calibration range

Up to 2017 inclusive:

- A maximum of 3 plasma-borne clinical cases of vCJD in any genotype group in recipients under the age of 76 that have been un- or misdiagnosed.

Platelet model calibration range

Up to 2017 inclusive:

- A maximum of 3 platelet-borne clinical cases of vCJD in any genotype group in recipients under the age of 76 that have been un- or misdiagnosed.

For each blood component model, combinations of input parameters that produce numbers of clinical cases of vCJD that fall outside of these calibration ranges are discarded.

Results

To obtain the model estimates, the three component models are run under both the variable clinical attack rate and rapid onset scenarios until 30,000 calibrated runs are produced for each epidemiological scenario, i.e. 30,000 runs where the number of clinical cases of vCJD fall within the calibration ranges given above. The median, upper 95% credible interval (CI), and lower 95% CI of the estimated expected values for the number of infections and clinical cases over these 30,000 runs are then used.

Care must be taken when interpreting the results due to the following technical points: as we are calculating the median and 95% CI separately for different periods, the number of clinical cases and infections occurring before and after 2020 may not sum to the total over the whole period; for the graphs of the estimated number of clinical cases of vCJD each year, as the curves are the individual Monte Carlo runs that give the median and 95% CI for the total number of clinical cases (the area under the curves) the ordering of the runs within a given year may appear counter-intuitive, e.g. the upper 95% CI may be lower than the lower 95% CI in that year; and as the model produces expected values the number of infections and clinical cases estimated may not be whole numbers.

As the model and its calibration are both highly precautionary, it is likely that the estimated number of infections and clinical cases of vCJD will represent an overestimate and so will be lower in reality.

Red blood cells

In total the model assumes there will be around 200 million red blood cell transfusions between 1978 and 2070 with 90 million occurring from the end of 2019.

Table 2 Output of red blood cell model under the variable clinical attack rate (CAR) and rapid onset scenarios, values are medians (95% credible interval).

Model output	Variable CAR scenario	Rapid onset scenario
Infections, occurring before 2020	1,066 (99 – 6,370)	460 (83 – 2,607)
Infections, occurring between 2020 and 2070	230 (6 – 1,699)	101 (4 – 823)
Infections, total	1,349 (120 – 7,726)	571 (98 – 3,328)

Model output	Variable CAR scenario	Rapid onset scenario
Clinical cases, onset before 2020	20 (10 – 29)	21 (11 – 30)
Clinical cases, onset 2020 onwards	16 (3 – 43)	46 (7 – 210)
Clinical cases, total	36 (14 – 67)	67 (22 – 233)
Clinical cases caused by infections occurring between 2020 and 2070	7 (0 – 22)	13 (1 – 62)

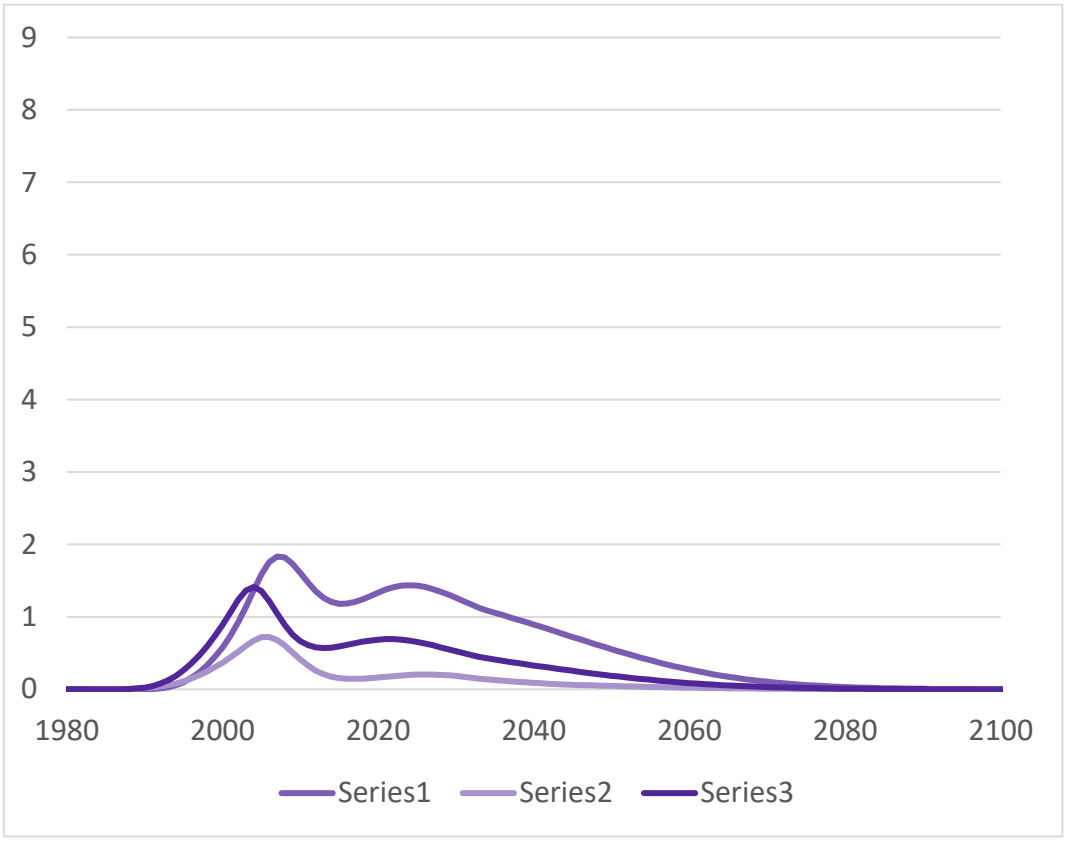
The model estimates that between 31% to 55% of clinical cases (21 of 67 under rapid onset and 20 of 36 under variable CAR) due to the transfusion of red blood cells have already occurred. Of those remaining, between 29% and 45% of the clinical cases of vCJD (13 of 46 under rapid onset and 7 of 16 under variable CAR) are due to future infections occurring over the next 50 years (roughly 20% of the total cases). Even under the upper 95% CI the future RBC-borne vCJD risk is minimal with an estimated 62 clinical cases due to infections from the 90 million transfusions occurring over the next 50 years.

Due to the highly precautionary nature of the model calibration, the estimated median number of clinical cases with onset before 2020 of around 20 is much greater than the 3 cases seen to date (which is closer to the lower 95% CI). This disparity is due to the calibration range in which up to 7 clinical cases in those aged under 76 could have been un- or misdiagnosed combined with the potential for a large number of un- or misdiagnosed cases in recipients aged over 75.

While the estimated number of clinical cases due to future infections is relatively low in both epidemiological scenarios, the estimated number of future infections is high. This is due to the combination of: the precautionary assumption that all recipients are completely susceptible to infection; the long incubation periods and reduced recipient survival (infected individuals not surviving long enough for clinical symptoms to develop); and the possibility of a very low clinical attack rate in the variable CAR scenario. This low case to infection ratio is consistent with clinical cases of vCJD associated with dietary exposure in which, to date, 175 cases appear to have occurred in approximately 30,000 infected individuals (based on the results of the Appendix II study).

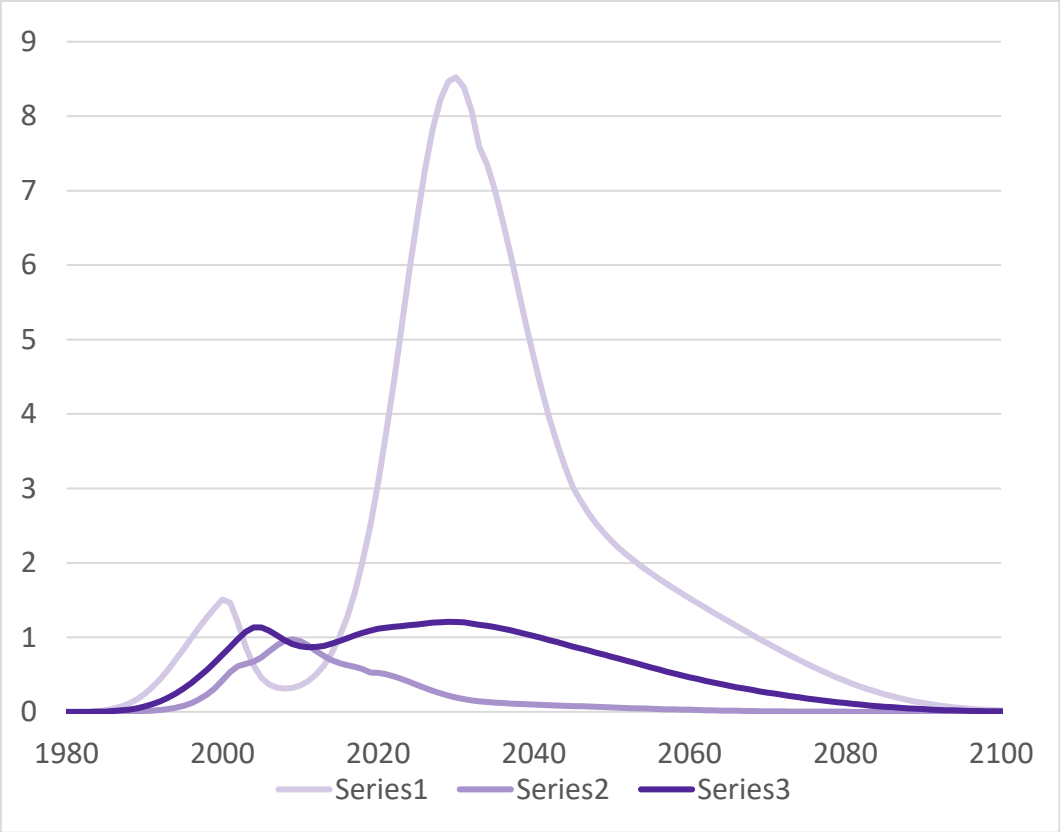
It is important to note the extremely wide credible intervals on all estimates of the model reflecting the inherent uncertainty in the input parameter and calibration ranges used. As asymptomatic infections cannot be diagnosed in living individuals, and so do not form part of the model calibration, their number are even more uncertain.

Figure 1 Estimated number of clinical cases of vCJD each year due to red blood cell transfusions under the variable clinical attack rate scenario. Curves are the individual Monte Carlo runs that give the median and 95% credible interval (CI) for the total number of clinical cases over the whole modelled period.



Under the variable clinical attack rate scenario (see Figure 1) in the median, lower 95% CI, and upper 95% CI model run outputs the estimated expected number of clinical cases each year remains low with at most 0.7 to 1.8 cases annually. In all outputs there are two peaks in the estimated number of clinical cases: an earlier higher peak due to the shorter incubation in the MM homozygote genotype group corresponding to the clinical cases which have already occurred; and a second smaller peak of clinical cases centred at some point between 2020 and 2030 and due to the longer incubation in the non-MM homozygote genotype groups. The outputs also exhibit long tails with up to 5% of clinical cases estimated as having an onset after 2060.

Figure 2 Estimated number of clinical cases of vCJD each year due to red blood cell transfusions under the rapid onset scenario. Curves are the individual Monte Carlo runs that give the median and 95% credible interval (CI) for the total number of clinical cases over the whole modelled period.



Under the rapid onset scenario (see Figure 2) in all but the upper 95% CI model run output the estimated expected number of clinical cases each year remains relatively low with at most 1.0 to 1.1 cases annually. As in the variable CAR scenario, all outputs show an initial peak in clinical cases corresponding to the cases which have already occurred. This peak is due to the shorter incubation in the rapid onset MM homozygote genotype group in the median and upper 95% CI outputs and due to a shorter incubation in all genotype groups in the lower 95% CI output. In addition to the initial peak, the median and upper 95% CI outputs also have secondary peaks centred at around 2030 due to the longer incubation of the remaining MM homozygote and non-MM homozygote genotype groups. While the secondary peak in the median output is low at 1.2 clinical cases annually, the upper 95% CI output has both a larger initial peak of 1.5 clinical cases per year centred at around 2000 and a much larger secondary peak of 8.5 clinical cases per year. This large future peak leads to an estimated 206 clinical cases with onset after 2019. Such a number seems unlikely, however, as it requires that 27 cases of vCJD have already occurred but been un- or misdiagnosed and that the rapid onset MM homozygote subgroup (if it does indeed exist) represent less than 1% of the UK population. It is also worth noting that of the 206 clinical cases with onset after 2019 only 32 would be due to future infections.

Again all the model outputs exhibit long tails with up to 5% of clinical cases estimated as having an onset after 2069.

Plasma

In total the model assumes there will be around 33 million UK sourced plasma transfusions (single unit equivalent) between 1978 and 2070 with 14 million occurring from the end of 2019.

Table 3 Output of plasma model under the variable clinical attack rate (CAR) and rapid onset scenarios, values are medians (95% credible interval).

Model output	Variable CAR scenario	Rapid onset scenario
Infections, occurring before 2020	188 (6 – 907)	107 (4 – 562)
Infections, occurring between 2020 and 2070	71 (1 – 322)	46 (1 – 277)
Infections, total	271 (9 – 1,139)	155 (6 – 795)
Clinical cases, onset before 2020	2 (0 – 6)	3 (0 – 7)
Clinical cases, onset 2020 onwards	4 (0 – 40)	19 (1 – 87)
Clinical cases, total	6 (0 – 44)	22 (1 – 92)
Clinical cases caused by infections occurring between 2020 and 2070	1 (0 – 18)	6 (0 – 31)

The model estimates that between 13% to 37% of clinical cases (3 of 22 under rapid onset and 2 of 6 under variable CAR) due to the transfusion of plasma (FFP and cryoprecipitate) have already occurred. Of those remaining, between 30% and 41% of the clinical cases of vCJD (6 of 19 under rapid onset and 1 of 4 under variable CAR) are due to future

infections occurring over the next 50 years (roughly 24% of the total cases). Even under the upper 95% CI the future plasma-borne vCJD risk is low with an estimated 31 clinical cases due to infections from the 14 million transfusions (single unit equivalent) occurring over the next 50 years.

While the number of clinical cases due to future infections is lower than for RBCs this is in part due to the approximate six-fold lower number of UK sourced units of plasma transfused. This greater relative risk is due to the lack of observed clinical cases with which to calibrate the plasma model meaning it is less constrained and allowing for larger future peaks. The estimated number of clinical cases with onset before 2020 of around 2 to 3, while greater than the 0 cases seen to date which is closer to the lower 95% CI, does not appear unreasonable.

In a similar manner to the output of the RBC model, there is a low clinical case to infection ratio due to the precautionary assumptions and all values have extremely wide credible intervals reflecting the great uncertainty in the input parameter and calibration ranges used.

Figure 3 Estimated number of clinical cases of vCJD each year due to plasma transfusions under the variable clinical attack rate scenario. Curves are the individual Monte Carlo runs that give the median and 95% credible interval (CI) for the total number of clinical cases over the whole modelled period.

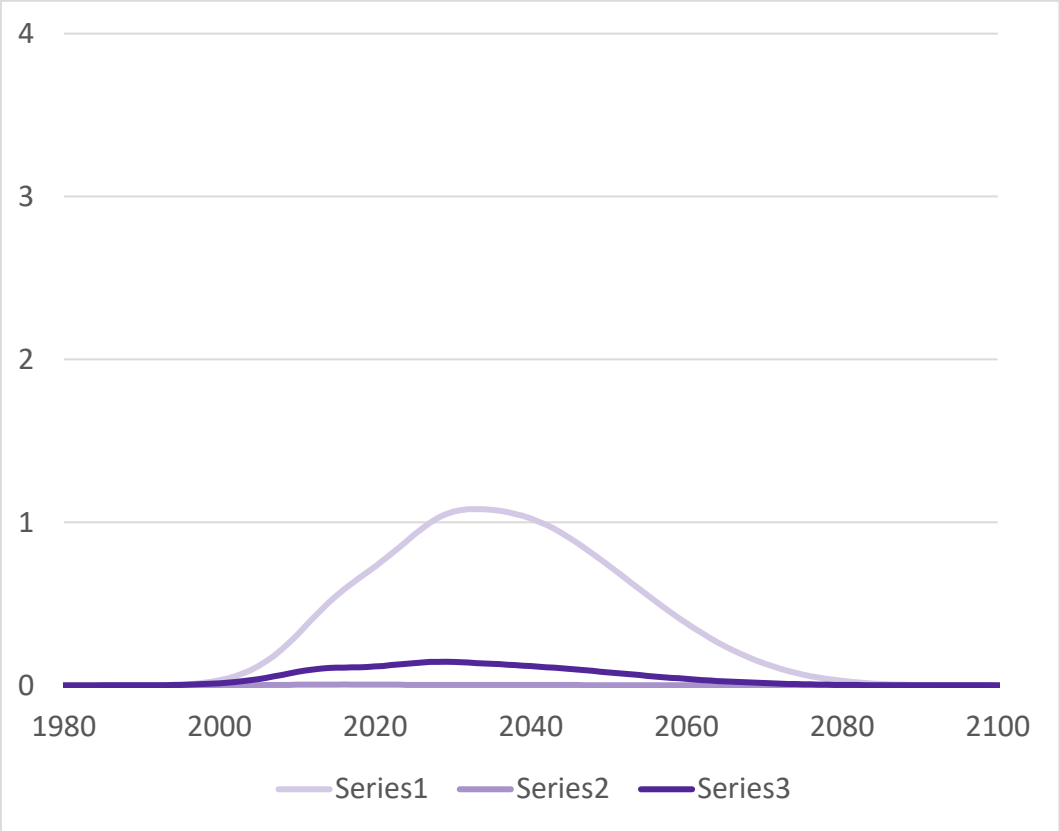
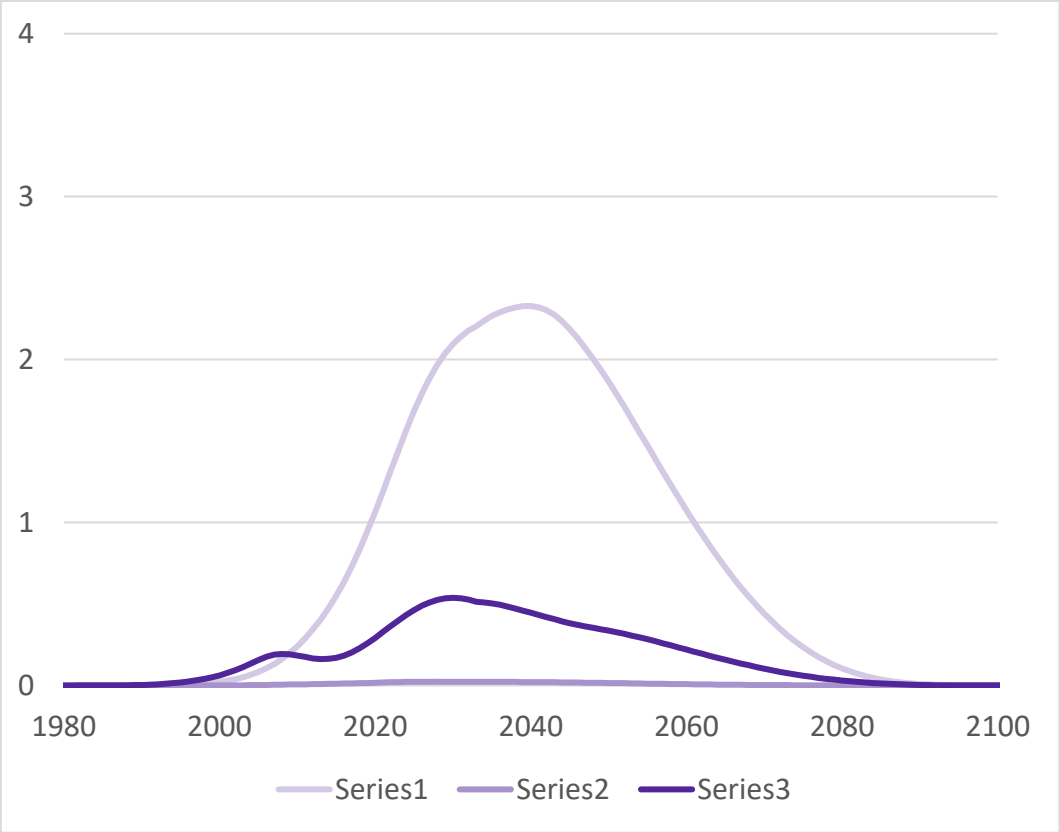


Figure 4 Estimated number of clinical cases of vCJD each year due to plasma transfusions under the rapid onset scenario. Curves are the individual Monte Carlo runs that give the median and 95% credible interval (CI) for the total number of clinical cases over the whole modelled period.



Under both epidemiological scenarios (see Figure 3 and Figure 4) all median and upper 95% CI model run outputs show roughly a single peak centred between 2029 and 2039 (the median rapid onset does appear to have an initial plateau between 2008 and 2017 but this is small at 0.2 clinical cases annually) due to the combination of clinical cases in all genotype groups. These peaks are relatively small at between 0.1 and 1.1 clinical cases annually under the variable CAR scenario and between 0.5 and 2.3 cases under the rapid onset scenario. The lower 95% CI model run outputs show almost no clinical cases across the entire modelled period. Again the median and upper 95% CI model outputs exhibit long tails with up to 5% of clinical cases estimated as having an onset after 2068.

Platelets

In total the model assumes there will be around 31 million platelet transfusions (of which approximately 50% are apheresis) between 1978 and 2080 with 19 million occurring from the end of 2019.

Table 4 Output of platelet model under the variable clinical attack rate (CAR) and rapid onset scenarios, values are medians (95% credible interval).

Model output	Variable CAR scenario	Rapid onset scenario
Infections, occurring before 2020	259 (6 – 1,867)	163 (5 – 1,125)
Infections, occurring between 2020 and 2080	145 (2 – 1,104)	107 (1 – 899)
Infections, total	429 (10 – 2,756)	275 (8 – 1,975)
Clinical cases, onset before 2020	3 (0 – 7)	4 (0 – 10)
Clinical cases, onset 2020 onwards	5 (0 – 55)	25 (1 – 162)
Clinical cases, total	8 (0 – 61)	29 (1 – 169)
Clinical cases caused by infections occurring between 2020 and 2080	3 (0 – 32)	12 (0 – 84)

The model estimates that between 13% to 33% of clinical cases (4 of 29 under rapid onset and 3 of 8 under variable CAR) due to the transfusion of platelets (apheresis and pooled) have already occurred. Of those remaining, between 46% and 56% of the clinical cases of vCJD (12 of 25 under rapid onset and 3 of 5 under variable CAR) are due to future infections occurring over the next 60 years (roughly 36% to 39% of the total cases). Under the upper 95% CI the future platelet-borne vCJD risk is moderate with an estimated 84 clinical cases due to infections from the 19 million transfusions occurring over the next 60 years. Relative to the plasma model, the higher number and proportion of clinical cases due to future infections is because of the greater proportion of pooled platelets, which have a greater donor exposure and so greater risk, assumed to be issued in future. The estimated number of clinical cases with onset before 2020 of around 3 to 4, while greater than the 0 cases seen to date which is closer to the lower 95% CI, does not appear unreasonable.

In a similar manner to the output of the RBC and plasma models, there is a low clinical case to infection ratio due to the precautionary assumptions and all values have extremely wide credible intervals reflecting the great uncertainty in the input parameter and calibration ranges used. In a similar manner to plasma, the model is also likely to produce wider estimates than the RBC model due to the lack of clinical cases for calibration constraining the model.

Figure 5 Estimated number of clinical cases of vCJD each year due to platelet transfusions under the variable clinical attack rate scenario. Curves are the individual Monte Carlo runs that give the median and 95% credible interval (CI) for the total number of clinical cases over the whole modelled period.

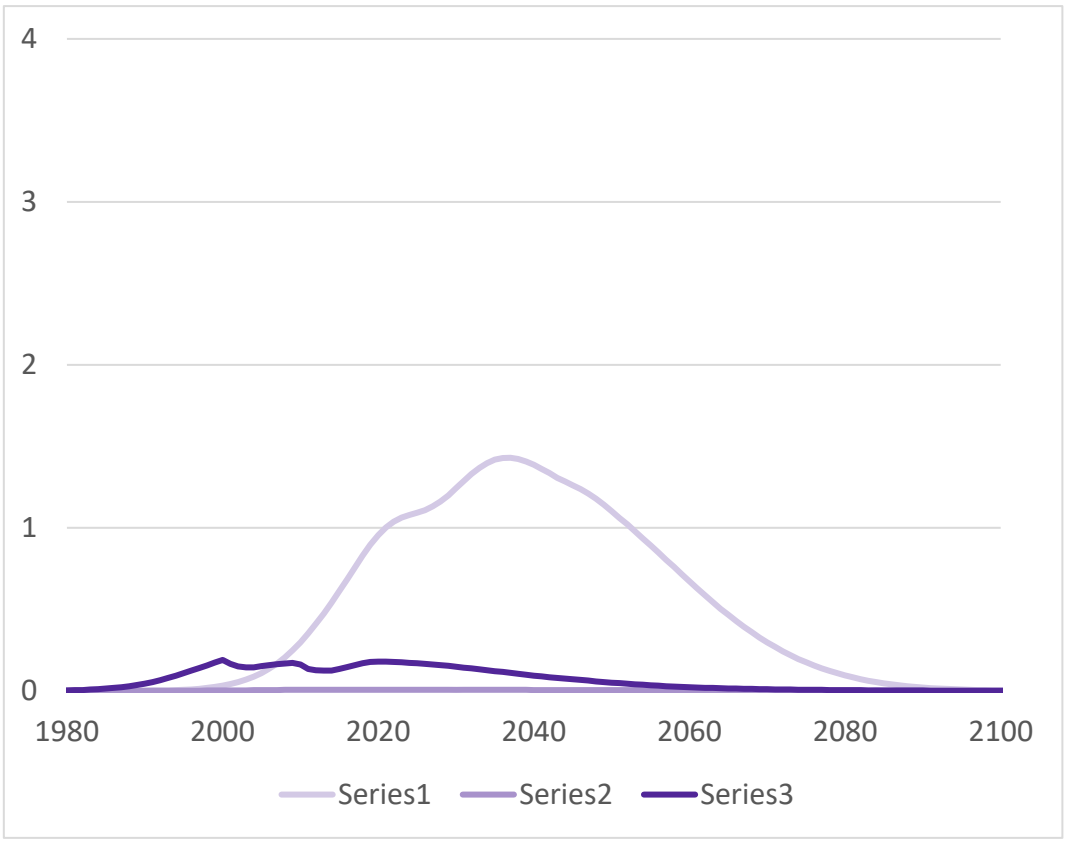
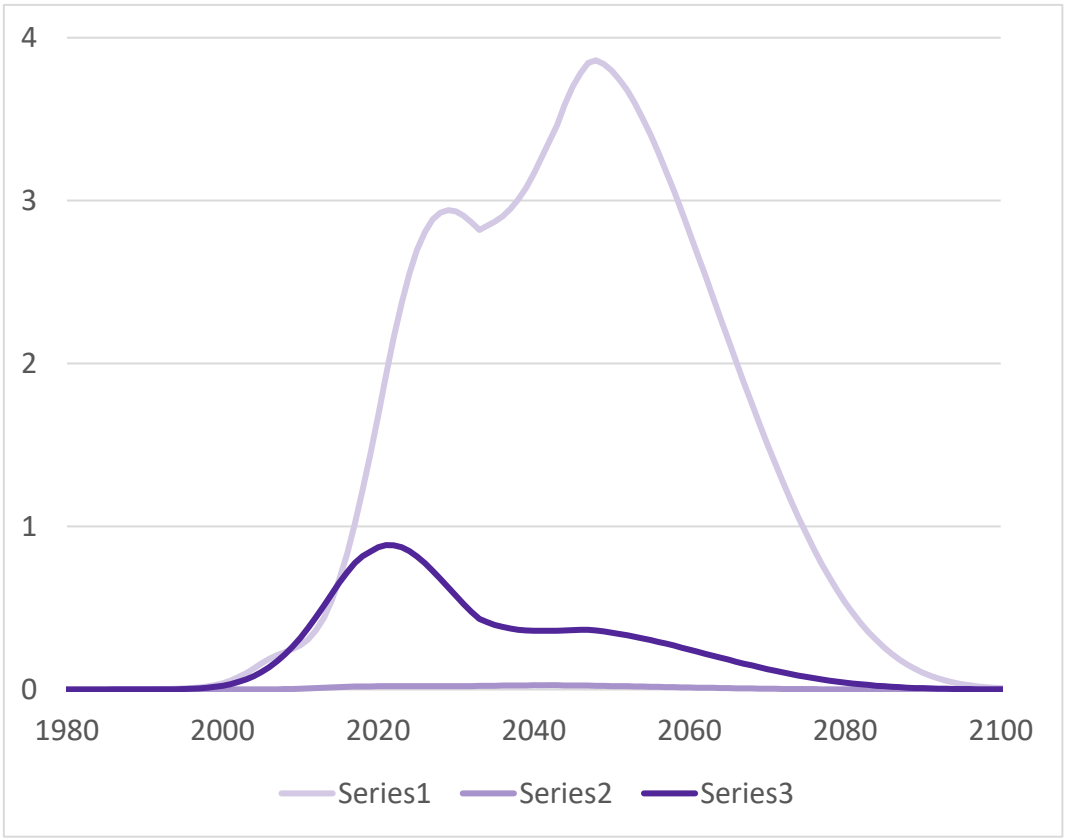


Figure 6 Estimated number of clinical cases of vCJD each year due to platelet transfusions under the rapid onset scenario. Curves are the individual Monte Carlo runs that give the median and 95% credible interval (CI) for the total number of clinical cases over the whole modelled period.



The distribution of clinical cases in the median and upper 95% CI model runs under both epidemiological scenarios (see Figure 5 and Figure 6) broadly show a similar pattern to that of plasma, with a single peak due to the combination of clinical cases in all genotype groups but with some additional jaggedness. This jaggedness is caused by the changes in the proportion of apheresis platelets issued leading to a corresponding change in the number of donor exposures and so the number of infections each year. Between 2008 and 2010 the proportion of apheresis issues rose from around 40% to around 80% it then remained steady between 2010 and 2013 before falling again to around 50% by 2017.

In the median run under the variable CAR scenario the number of clinical cases stays relative flat at around 0.2 cases per year between 1998 and 2029 while the upper 95% CI run has a single distinct peak of 1.4 clinical cases annually centred at 2037. Under the rapid onset scenario the jaggedness causes both the median and upper 95% CI model runs to exhibit two peaks in clinical cases. The median run has an initial peak of 0.9 clinical cases per year centred at 2026 and another smaller plateau of 0.4 between 2036 and 2050 while the upper 95% CI run has an initial peak of 2.9 cases centred at 2029 and a larger secondary peak of 3.9 centred at 2048. Again the lower 95% CI model run outputs under both scenarios show almost no clinical cases across the entire modelled period and

all outputs exhibit long tails with up to 5% of clinical cases estimated as having an onset after 2074.

Discussion

The DHSC model does not attempt to capture every aspect of vCJD and instead concentrates on the factors that most affect the broad pattern of infections and clinical cases. It is intended to provide a reasonable precautionary estimate that can be used to assess the potential benefit of risk mitigation measures.

The model makes several precautionary assumptions, meaning it is more likely to over- than underestimate the number of infections and clinical cases of vCJD. It assumes:

- there is a subclinical carrier state present in the UK population who transmit their infection via blood and that the more precautionary interpretation of the Appendix III study is correct.

- the number of issues of each component is the same as usage and that each of these units is transfused to a separate recipient, maximising the number of recipients exposed to any risk.

- that all recipients are completely susceptible to infection and that these infections are equally likely to develop into clinical cases regardless of genotype.

- that the risk in MV heterozygotes and VV homozygotes is the same even though VV is believed to be less risky.

- when calibrating, that there is a high level of under-ascertainment of clinical cases whilst also not limiting the number of cases in individuals aged over 75 years old.

Even given these precautionary assumptions, the revised model estimates far fewer clinical cases of vCJD due to future infections then was estimated by the previous risk assessment in 2013:

- For red blood cells, the model estimates 7 to 13 (range 0 to 62) clinical cases due to infections from the 90 million transfusions modelled as occurring over the next 50 years.

- For plasma, the model estimates 1 to 6 (range 0 to 31) clinical cases due to infections from the 14 million (single unit equivalent) transfusions modelled as occurring over the next 50 years.

- For platelets, the model estimates 3 to 12 (range 0 to 84) clinical cases due to infections from the 19 million transfusions modelled as occurring over the next 60 years.

These estimates are supported by ACDP TSE Sub Group as, while uncertain and subject to revision in the light of further data, to be of the right order of magnitude. The decrease from the previous 2013 estimates are due to both the revised assumptions and also changes to the input parameter and calibration ranges agreed by ACDP TSE Sub Group. These were needed in part to account for the greater number of years that have past pass without further blood-borne cases of vCJD but also to account for new evidence on the possible prevalence of subclinical carriers and on the relative infectivity of plasma and platelet components with and without leucodepletion.

While the model estimates few clinical cases of vCJD, there is still the potential for a large number of infections due to secondary transmission (most of which will never present as clinical cases). This result should be considered critically as it is due in part to the precautionary assumption of complete susceptibility to infection in recipients but also to the fact that the number of infections cannot form part of the model calibration. The number of infections though high is still small compared to the much larger number of silent dietary vCJD infections assumed in the modelling. Current scientific understanding is that individuals who remain asymptomatic suffer no apparent harm and, due to the ban on recipients donating, there is no potential for vCJD infections to become self-sustaining by this route.

The uncertainties in our basic understanding of vCJD present a fundamental difficulty in assessing the risk posed by blood-borne transmissions. As this model is both precautionary and uses large input and calibration ranges it will inevitably produce extremely wide estimates with high upper bounds. Thorough follow-up of “at risk” individuals and continued surveillance remain essential if evidence on vCJD risks is to accumulate. This will help to reduce the uncertainty and so this risk assessment model will need to be updated as and when new information becomes available.

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Appendix 1 Data used in the DHSC model

Table 5 Historic makeup of whole blood and apheresis donor populations by age at time of donation. Data based on studies by UK Blood Services and assumed to remain constant across the modelled period.

Donor age group	Proportion of whole blood donations	Proportion of apheresis donations
<16	0%	0%
16-20	7%	1%
21-30	16%	7%
31-40	27%	13%
41-50	26%	32%
51-60	19%	32%
61-70	5%	15%
71-80	0%	0%
>80	0%	0%
Total	100%	100%

Table 6 Proportion of acute and chronic recipients of red blood cell by age group. Acute recipients undergo a "one-off" transfusion of red blood cell units while chronic recipients receive regular transfusions (see main text for further details). Values were derived from 2014 National Red Cell Survey for RBCs.

Recipient age group	Acute	Chronic
<28 days	1.2%	0.0%
29 days - <1 year	0.5%	0.1%
1-15	0.6%	1.7%
16-30	3.8%	3.0%
31-40	3.7%	2.9%
41-50	3.5%	4.4%

Recipient age group	Acute	Chronic
51-60	4.5%	6.3%
61-74	10.2%	15.2%
75+	15.5%	22.8%
Total	43.5%	56.5%

Table 7 Proportion of acute and chronic recipients of plasma by age group. Acute recipients undergo a "one-off" transfusion of plasma units while chronic recipients receive regular transfusions (see main text for further details). Values were derived by combining 2009 Audit of the use of Fresh Frozen Plasma with 2013 - 2018 patterns of usage provided by the Scottish National Blood Transfusion Service (SNBTS).

Recipient age group	Acute	Chronic
<28 days	1.5%	1.0%
29 days - <1 year	0.3%	0.2%
1-15	1.4%	0.6%
16-30	5.6%	2.1%
31-40	4.4%	3.2%
41-50	6.7%	5.5%
51-60	9.0%	6.9%
61-74	18.4%	10.9%
75+	16.4%	6.1%
Total	63.7%	36.3%

Table 8 Proportion of acute and chronic recipients of platelets by age group. Acute recipients undergo a "one-off" transfusion of platelet units while chronic recipients receive regular transfusions (see main text for further details). Values were derived by combining data from 2001 EASTR study (see [Wells 2009]) with 2013 - 2018 patterns of usage provided by the Scottish National Blood Transfusion Service (SNBTS).

Recipient age group	Acute	Chronic
<28 days	1.1%	1.4%
29 days - <1 year	0.4%	0.7%
1-15	1.1%	6.6%
16-30	2.7%	7.5%
31-40	2.6%	6.6%
41-50	3.7%	10.0%
51-60	4.2%	14.7%
61-74	5.6%	16.3%
75+	4.4%	10.4%
Total	25.8%	74.2%

Table 9 Annual issues of blood components for the UK (values in thousands). Number of issues are sourced from Serious Hazards of Transfusion annual reports with different plasma units converted to their singe unit equivalents, and the proportion of platelets that are apheresis units assumed to be the same as values provided by England's NHS Blood and Transplant (NHSBT).

Year	Red blood cells	Plasma	Pooled platelets	Apheresis platelets
2000 and earlier	2,800	460	150	100
2001	2,800	470	150	100
2002	2,700	470	160	100
2003	2,700	470	160	100

Year	Red blood cells	Plasma	Pooled platelets	Apheresis platelets
2004	2,700	470	160	110
2005	2,500	420	160	110
2006	2,400	430	160	110
2007	2,300	420	160	110
2008	2,200	410	160	110
2009	2,300	430	110	160
2010	2,200	470	50	200
2011	2,200	490	60	250
2012	2,200	500	60	260
2013	2,100	490	60	260
2014	2,000	460	90	240
2015	1,900	450	120	200
2016	1,900	440	130	190
2017 and later	1,800	450	160	160

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