Risk of variant Creutzfeldt–Jakob disease transmission by blood transfusion in Australia

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Abstract

Background and Objectives: Most of the 233 worldwide cases of variant Creutzfeldt–Jakob disease (vCJD) have been reported in the United Kingdom and 3 have been associated with transfusion-transmission. To mitigate the potential vCJD risk to blood safety, Australian Red Cross Lifeblood imposes restrictions on blood donation from people with prior residency in, or extended travel to, the United Kingdom during the risk period 1980–1996. We have modified a previously published methodology to estimate the transfusion-transmission risk of vCJD associated with fresh component transfusion in Australia if the UK residence deferral was removed.

Materials and Methods: The prevalence of current pre-symptomatic vCJD infection in the United Kingdom by age at infection and genotype was estimated based on risk of exposure to the bovine spongiform encephalopathy agent for the period 1980–1996. These results were used to estimate the age-specific prevalence of undiagnosed, pre-symptomatic vCJD in the Australian population in the current year due to prior UK residency or travel. The primary model outputs were the 2020 vCJD risks/unit of vCJD contamination, transfusion-transmission (infections) and clinical cases.

Results: The overall (prior UK residency in and travel to United Kingdom, 1980–1996) mean risk of contamination per unit was 1 in 29,900,000. The risks of resulting vCJD transmission (infection) and clinical case were 1 in 389,000,000 and 1 in 1,450,000,000, respectively.

Conclusion: Our modelling suggests that removing the Lifeblood donation deferral for travel to, or UK residence, would result in virtually no increased risk of vCJD transfusion-transmission and would be a safe and effective strategy for increasing the donor base.
INTRODUCTION

Variant Creutzfeldt–Jakob disease (vCJD) is a human transmissible spongiform encephalopathy first reported in 1996 [1]. Pathogenesis is associated with an abnormal infectious isoform of the naturally occurring cellular prion sialoglycoprotein PrPc. The abnormal isoform, which does not contain nucleic acid, is designated as PrPRES, PrPsc, or PrP^{TSE}. The origin of the prion strain associated with vCJD is the strain associated with bovine spongiform encephalopathy (BSE) in cattle [2, 3]. Infection with vCJD is universally fatal, and there is no effective treatment to control or cure vCJD [1].

Following infection, there is an extended pre-symptomatic period, which, although not well defined, is estimated at 10–16 years for primary vCJD for UK cases (modelled range: 8–55 years depending on the genotype) [4–6].

vCJD has primarily occurred in the United Kingdom (178 of 233 cases worldwide to March 2021) with only 55 cases in 11 countries recorded outside that country (Figure 1). The peak of the UK epidemic occurred in 2000 (28 deaths), and none of the 178 cases is alive [8]. The primary route of human infection is through dietary consumption of beef from cattle infected with BSE over the period 1980–1996 associated with contaminated stock feed [1, 9].

FIGURE 1  Reported cases of variant Creutzfeldt–Jakob disease worldwide. Source: https://www.eurocjd.ed.ac.uk/data and 2020 case report [7].
The primary route of infection via beef consumption in the United Kingdom (and other European countries) was reportedly eliminated by industry regulation from 1996. However, three human cases of vCJD transmission associated with transfusion have been reported [10–12], as well as a potential sub-clinical case diagnosed at post-mortem following death from an unrelated condition [13], all in the United Kingdom, involving non-leucodepleted red blood cells transfused between 1996 and 1999. Additionally, there is a single report of possible transmission of vCJD by plasma-derived products [14].

Animal experiments support that vCJD infectivity in blood is highly associated with leucocytes [15, 16], and therefore leucodepletion is an effective measure in reducing the risk of vCJD. Accordingly, leucodepletion was an early risk minimization strategy, introduced in the United Kingdom in 1999 [17] and in Australia in 2008 (Australian Red Cross Lifeblood, hereafter Lifeblood, unpublished). The proportion of vCJD infectivity removed by leucodepletion of human blood is not well defined but data from animal model suggest it as 42%–71% [15, 16].

Because of the potential risk of secondary infection via transfusion, many countries have imposed restrictions on blood donation from people with potential exposure risk through prior residency in, or extended travel to, the United Kingdom and/or other countries recording vCJD cases [18]. Under regulations current in 2022, Lifeblood defers from donation individuals who have resided in/visited the United Kingdom for a cumulative period exceeding 6 months within the period 1980–1996. The current predicted impact is the loss of 3.5% (approx. 57,000) donations annually (see Data S1 and S2). This policy remains in effect due to continuing uncertainty about disease pathogenesis and transmission, despite the absence of local cases [19], and reports of international transfusion-transmission after 1999 [20]. Although the primary epidemic peak appears to have passed, there remains concern about potential further cases associated with PRNP genotypes MV and VV at codon 129. These cases may have longer disease incubation periods compared to the MM genotype, which was present in 42% of a sample of UK blood donors [21] and represented all genotyped vCJD cases reported before 2016. MV heterozygous and VV homozygous individuals with accumulation of prion protein have been identified by retrospective tonsil/appendix tissues [22–25], as well as in a recipient of non-leucodepleted red blood cells (RBCs) who died 5 years later from unrelated causes [13]. In addition, the last case of vCJD identified in the United Kingdom (2016) was MV heterozygous [26], adding to concerns of a potential second wave of vCJD [18].

Blood services use risk tolerability principles to balance risk minimization to blood recipients with sufficiency of blood supply, which requires ongoing assessment of donor eligibility criteria [27, 28]. In this context, deferral of donors who present negligible transfusion-transmission risk is not consistent with a risk-based approach to blood safety and may present a threat to the blood supply. Lifeblood uses an internal framework for determining the tolerable transfusion risk level based on the Alliance of Blood Operators Risk Based Decision Making Framework, which acknowledges that risk cannot be reduced to zero but should be as low as reasonably achievable while maintaining sufficiency of supply [29]. Lifeblood has determined that the tolerability threshold for an agent classified as posing a threat of ‘catastrophic severity’, such as vCJD, is ‘tolerable’ if kept below 1 in 5 million per unit transfused.

Concerns over the potential for a second wave of vCJD and the lack of an effective treatment are potential reasons for the relative lack of widespread policy change around vCJD transfusion risk [18, 20]. However, recently the US Food and Drug Administration (FDA) amended and removed some of its vCJD-related geographical deferrals [30], and Ireland became the first country to lift a vCJD deferral for past UK residents [31]. Notably, the United Kingdom has also rescinded its precautionary vCJD risk reduction measure requiring the use of imported plasma and apheresis platelets for individuals born or after 1 January 1996 and/or with thrombocytopenia [31], and, most recently, announced it would lift its 1998 ban on fractionating locally sourced plasma [17, 32]. Review of deferral policy in the United States by the FDA has been guided by stochastic risk assessments modelling a range of risk scenarios, including those with extended incubation periods [5].

We adopted the FDA methodology for red cell transfusion risk [5] to develop a vCJD risk model for transfusion of fresh components including red cells, platelets, and clinical plasma in Australia. Our aim was to estimate the risk of vCJD transmission in Australia should the UK residence deferral be discontinued.

### METHODS

#### Australian exposure assessment model

An overview of the simulation model process used to estimate vCJD transmission risk is shown in Figure 2, with specific input parameters listed in Table 1 and technical detail provided in Data S1.

We applied a very similar methodology to that used by the FDA to estimate the prevalence of undiagnosed pre-symptomatic vCJD in the Australian population (Figure 2: Stage 1a). We based our modelling on published stochastically modelled UK prevalence estimates (100 asymptomatic undiagnosed cases in 2011, equivalent prevalence of 1.7/million) [6], which are broadly consistent with outbreak numbers [8]. We assumed no change in prevalent undiagnosed, pre-symptomatic vCJD cases. Relative risk according to year and duration of exposure during 1980–1996 was based on relative risk of UK BSE cases per given year (Table S2) [37]. These data were used to develop estimates of the current age-specific prevalence of undiagnosed pre-symptomatic vCJD in the United Kingdom by calendar year and duration of exposure. The age distribution of prevalent undiagnosed pre-symptomatic vCJD for MM genotypes was based on observed cases to 2003 (Table S1) [23] and adjustment was made to incorporate a longer estimated incubation time for non-MM genotypes (35 years) (Table 1) [5, 6, 21, 33–35].

Outputs were generated through Monte Carlo simulation using at least 10,000 replications, or convergence to 1% level of deviance for all output parameters (Figure S1) using Stata statistical software.
Where sufficient data was available, and unless otherwise specified, parameter inputs were drawn from assumed triangular distributions, which concentrate simulated outputs about the mean and which have restricted ranges of risk and are therefore not strongly affected by extreme simulated values.

**Outputs**

Primary outputs were the 2020 risks of (1) vCJD contaminated unit, (2) vCJD transfusion-transmission, and (3) case of clinical vCJD (infection resulting in disease).

We estimated exposure risk associated with time spent in the United Kingdom but not in the rest of Europe since Lifeblood restricted deferral to UK residence only. Because no donor-specific exposure data were available, exposure risk in the general population was used based on Australian Bureau of Statistics (ABS) population data, while blood donor numbers were based on Lifeblood internal data (Figure 2, Stage 1b). This approach assumes that the annual age-specific vCJD prevalence in donors is equal to that of the Australian general population. We estimated prevalence separately for both travellers to the United Kingdom and for former UK residents currently living in Australia. An at-risk traveller to the United Kingdom was defined as a resident who spent time in that country during the risk period 1980–1996 and who has returned to Australia from the United Kingdom at some time before 2007 (up to 10 years after the end of the risk period). A former resident was defined as a person counted as living in Australia by usual place of residence who was born in the United Kingdom.

**Blood donor population**

Overall donor numbers were based on Lifeblood data 2014–2018 (Table S3) as well as Lifeblood projections for 2021–2025 (Table S4). We limited consideration of risk to donors of fresh blood components, given prion infectivity is substantially decreased during the fractionation process [42]. The age distribution of fresh component donors for each year was based on observed age-specific fresh component data for 2018 (Table S5). Annual age-specific frequencies of donation per donor were based on 2014–2018 donation frequency in all donors, which were extrapolated to later years 2019–2025 using linear regression. Annual age-specific donation rate per capita was then estimated based on ABS annual estimated resident population and projected population data [43, 44].

**Prior UK resident population**

Age-specific ABS census data on number of citizens with the United Kingdom as the country of birth by year of arrival were used to estimate the age-specific at-risk population of former residents for each calendar year by duration (6–12, 12–36, 36–60, and
>60 months) and period at risk 1980–1996 [45–47]. Because there was no detailed data on durations of exposure of less than a year, any exposure during 1980–1996 of less than a year was considered deferrable with duration ‘6–12 month’. Age-specific former resident proportions of census population totals by year and duration of exposure were scaled by ABS-estimated residential population numbers and projected population numbers to estimate final numbers at risk [43, 44]. Intercensal periods were interpolated, while projected populations were extrapolated and then adjusted for mortality using ABS life tables [48].

### TABLE 1 Major input distributions used in Australian exposure assessment model

| Parameter                                                                 | Selected value                                                                 | Simulation distribution | Source                                      |
|--------------------------------------------------------------------------|-------------------------------------------------------------------------------|-------------------------|---------------------------------------------|
| Primary exposed vCJD cases remaining at 2012-                            | Mean = 100 (95% CI [11–220])                                                  | Triangular              | Garske [6]                                  |
| (Sensitivity analysis) Appendix survey abnormal prion protein prevalence | Mean = 493 cases/million (95% CI [282–801]) cases/million                    | Triangular              | Gill [24]                                   |
| Prion protein genotype distribution                                      | MM: MV: VV 42%:47%:11%                                                        | Point estimates         | Nurmi [21]                                  |
| vCJD incubation (MM genotype)                                            | Mean = 15 years (90% CI [9–35])                                               | Log-normal              | Yang [5], Garske [6]                        |
| vCJD incubation (MV and VV genotypes)                                   | Mean = 35 years, (90% CI [23–55])                                             | Log-normal              | Yang [5], Garske [6], Collinge [33, 34], Kaski [35] |
| Age distribution of vCJD cases (MM)                                      | Table S1                                                                       | Point estimates         | Hilton [23]                                 |
| UK population by age group 2003                                          | Table S1                                                                       | Point estimates         | UK National Statistics [36]                 |
| Annual UK BSE cases 1980–1996                                           | Table S2                                                                       | Point estimates         | World Organization for Animal Health [37]   |
| Age- and year-specific frequency of blood donors 2014–2018               | Table S3                                                                       | Triangular using linear regression prediction 2020 | Lifeblood                                  |
| Projected fresh components donor numbers 2018–2025                       | Table S4                                                                       | Triangular using linear regression prediction 2020 | Lifeblood                                  |
| Age distribution of fresh components donors 2018                         | Table S5                                                                       | Point estimates         | Lifeblood                                  |
| Year-specific duration of travel to UK (1980–1996)                       | File S2                                                                        | Point estimates         | ABS (custom report)                         |
| Age specific distribution of travel                                       | Data table: ABS Cat. 3401                                                      | Point estimates         | ABS                                        |
| Age-specific Australian population (1980–2019)                           | Data table: ABS Cat. 3101059                                                   | Point estimates         | ABS                                        |
| Age-specific Australian population (2020–2060)                           | Data table: ABS Cat. 32220                                                    | Point estimates         | ABS                                        |
| Age-specific survival                                                     | Data table: ABS Cat. 3302055001                                               | Point estimates         | ABS Life tables 2016–2018                   |
| Repeat travel to the UK 1980–1996                                        | 61%                                                                           | Point estimate          | Seeteram [38]                              |
| Age, year of arrival specific Australian residents born in the United Kingdom | Data table 2006 Census: Persons by age, year of arrival and birthplace; 2011 Census: Persons by age, year of arrival and birthplace; 2016 Census: Persons by age, year of arrival and birthplace | Point estimate          | ABS                                        |
| Proportion of late incubation period infectious blood                     | Mode = 0.75 (min = 50% max = 0.90)                                            | Triangular              | Yang [5], Houston [39]                      |
| Infectious doses per unit of blood                                        | Mode = 0.09 (min = 0.01 max 0.14)                                             | Triangular              | Salamat [16]                               |
| Incubation for transfusion-transmitted case (MM)                          | Mean = 10 years (min = 6 max = 20)                                            | Triangular              | Bennet and Darachtchiev [40]                |
| Incubation for transfusion-transmitted case (MV and VV)                  | Mean = 20 years (min = 16 max = 30)                                            | Triangular              | Bennet and Darachtchiev [40]                |
| Post-transfusion survival rate                                            | Data S1, Function (genotype, incubation period)                                | Function                | Borkent-Raven [41]; ABS Lifetables          |
Prior UK traveller population

To estimate numbers of travellers at risk, we used an ABS custom-generated report of travellers returning from the United Kingdom by the duration of stay (<1, 2–3, 3–6, 6–12, 12–36, 36–60, and >60 months) and year of return to Australia (1980–2006) [49]. For returning travellers whose stay commenced prior to the start of the risk period (1980) or whose stay finished after the end of the risk period (1996), travel duration was reduced to reflect only the interval of travel at-risk (1980–1996). We developed an age distribution for these travellers based on ABS-published national travel data, which assumed constant age distribution by duration and year of travel [50]. We adjusted estimates by an index based on probability of repeat travel to the same destination by Australian travellers [38]. We assumed an average of two trips over the at-risk period for the proportion of travellers who repeatedly travelled where that travel was less than 1 year total duration, and an average of one trip if over 1 year duration.

Prevalence of vCJD in blood donors

Age- and genotype-specific prevalence estimates were applied to estimated Australian at-risk donor populations described above to estimate current age-specific prevalence of asymptomatic, undiagnosed infection in the Australian blood donor population (Figure 2, Stage 2a). Simulated genotype-specific vCJD incubation periods were drawn from log-normal distributions (Table 1) and adjusted by the proportion of the incubation period where blood was infectious to estimate the current number of asymptomatic donors who were infectious (Table 1; Figure 2, Stage 2b).

vCJD transmission risk

Donor prevalence data were used to estimate risks per unit of blood transfused for primary outputs:

- Risk of vCJD contamination ($P_{TT-vCJD,U}$), by estimating prevalence of vCJD–associated prion contamination per unit transfused based on age-specific donation frequencies and quantities in infected donors relative to the general donor population (Table 1; Figure 2, Stage 3a). This was calculated as the complement of the cumulative binomial probability of receiving no vCJD-infected blood ($B = 0$) during transfusion per unit transfused ($N_u = 1$) and given prevalence of infected units ($P_r$):

$$P_{TT-vCJD,U} = 1 - \text{Binomial distribution} \left( B = 0, N_u = 1, P_r \right)$$

- Risk of vCJD transfusion-transmitted infection, by scaling the risk of vCJD prions by simulated probabilities of infectious dose per unit transfused (Table 1; Figure 2, Stage 3b) [16].

- Risk of clinical vCJD, by scaling risk of vCJD infection by simulated probabilities of post-transfusion survival beyond the genotype-specific TT-vCJD incubation period (Table 1; Figure 2, Stage 3c) [40, 41].

Sensitivity analysis

The sensitivity of estimates to changes in assumptions about distributions of model parameters was evaluated. Specifically, low (2.5th percentile) and high (97.5th percentile) bounds on parameter distributions were sequentially used as fixed parameter values and model estimates generated as for the primary analysis using Monte Carlo simulation.

Detailed assessment of the sensitivity of estimates to changes in assumed prevalence of undiagnosed vCJD infections was conducted. We plotted the distribution of vCJD risk using the range of prevalences from the lower half of the distribution generated by Garske and Ghani [11–100 future cases] [6].

Because of theoretical concerns of potentially higher UK vCJD infectivity prevalence suggested by the UK Appendix surveys, we conducted additional analyses using the higher prevalence estimate of 493 cases per million (95% CI [282–801]) derived from the Appendix II survey results and as used in the FDA ‘high-prevalence’ analysis [5, 24, 25, 51].

To validate model findings, we estimated the cumulative total number of transfusion-transmitted cases expected to have arisen in Australia over the period 1980–2020 using both the Garske-modelled prevalence, as well as the Appendix II-based prevalence used in sensitivity analyses. We adjusted model parameters to account for the impact of the implementation of the donation deferral in December 2000 and the national implementation of leucodepletion for RBC and platelets in October 2008. Model outputs were also used to estimate the total number of clinical cases in Australia associated with primary exposure for the period 1980–2020 under both prevalence assumptions (see Data S1 for methodological details).

RESULTS

Donation

Donor numbers exposed to risk

The predicted number of donors providing fresh blood components for 2020 was 395,625. Of these donors, 14,016 (3.5%) met UK deferral criteria, comprising 9145 (2.3%) deferrable due to prior UK residency (2.0% donation rate from 448,372 individuals in general population with deferrable prior UK residency) and 4871 (1.2%) due to prior travel to the United Kingdom (1.7% donation rate from 288,740 individuals in general population with deferrable UK travel). The potential eligible donor population increase associated with ending the deferral was 737,112 (Table S6).
Predicted vCJD risk in donors

Mean predicted number of donors with vCJD in 2020 was 0.015 (2.5th–97.5th percentile: 0–0). A donation from a person with vCJD was predicted to occur once every 65 years (i.e. based on the same conditions as 2020). This risk was higher in donors with prior residency (1 in 70 years of donation) than for donors with travel-related exposure (1 in 900 years).

Transfusion

The risk of vCJD-contaminated donations, transfusion-transmissions and clinical cases of vCJD are presented in Table 2. Mean risk of contamination per unit was 1 in 30,000,000, the risk of vCJD transmission (infection) was 1 in 389,000,000 and the risk of a clinical case in a recipient (vCJD transfusion-transmission) was 1 in 1,450,000,000.

Sensitivity analysis

The results of the importance analysis indicated that the infectious dose per transfused unit and prevalence of vCJD infections in the United Kingdom had the most impact on the risk estimates for vCJD cases per unit of blood transfused in 2020 (Figure 3).

Sensitivity of estimated vCJD infection risk to change in assumed prevalence

Change in assumed prevalence of pre-symptomatic vCJD infection from 11 to 100 cases was associated with an increase in vCJD transmissions from less than 1 in $1.5 \times 10^{10}$ to 1 in $1.6 \times 10^9$ for prior resident donation exposure; and from less than 1 in $2.1 \times 10^{11}$ to 1 in $1.4 \times 10^{10}$ for travel-related donation exposure (Figure 4). Risk of a clinical case in a recipient (vCJD transfusion-transmission) based on the Appendix II-based prevalence estimate was 1 in 5,240,000 (Table S7). The model predicted 0.04 cases of TT-vCJD (2.5th–97.5th percentile, 0–0) for the period 1980–2020, with 1.1 cases (2.5th–97.5th percentile, 0–0) in the Australian population for the same period associated with primary exposure. Sensitivity analysis based on the Appendix II-based prevalence assumption predicted 8.0 cases of TT-vCJD (2.5th–97.5th percentile, 0–46), with 368 cases in the Australian population (2.5th–97.5th percentile, 0–1408) (Table S8).

TABLE 2  Mean vCJD risk in 2020 by risk exposure group

| Risk                        | Exposure group        | Mean (2.5th–97.5th percentile) | Point estimate (1 in x) |
|-----------------------------|-----------------------|--------------------------------|-------------------------|
| vCJD contamination/unit     | Prior UK resident 1980–1996 | $3.00 \times 10^{-6}$ (0–0)  | 33,000,000              |
|                             | Travel to UK 1980–1996  | $3.34 \times 10^{-9}$ (0–0)  | 299,000,000             |
|                             | Total                 | $3.34 \times 10^{-8}$ (0–0)  | 29,900,000              |
| vCJD transfusion-transmission/unit | Prior UK resident 1980–1996 | $2.30 \times 10^{-9}$ (0–0)  | 435,000,000             |
|                             | Travel to UK 1980–1996  | $2.69 \times 10^{-10}$ (0–0) | 3,720,000,000           |
|                             | Total                 | $2.57 \times 10^{-9}$ (0–0)  | 389,000,000             |
| Clinical vCJD/unit          | Prior UK resident 1980–1996 | $6.16 \times 10^{-10}$ (0–0) | 1,620,000,000           |
|                             | Travel to UK 1980–1996  | $7.20 \times 10^{-11}$ (0–0) | 13,900,000,000          |
|                             | Total                 | $6.88 \times 10^{-10}$ (0–0) | 1,450,000,000           |

**DISCUSSION**

Our modelling suggests that removing the UK residence deferral in Australia would result in virtually no increased risk of vCJD transfusion-transmission to recipients. In sensitivity analyses based on lower assumed prevalence, consistent with observed global case numbers, we found even lower risk. Risk will also reduce further as donors meeting current exclusion criteria exceed age thresholds for blood donation.

![Figure 3](https://example.com/image3.png)

**FIGURE 3** Importance analysis of input parameters to estimated annual number of future cases arising from infected Australian donors in 2020, for all blood fractions and combined travel and residency exposure groups. Analysis based on Monte Carlo models using 10,000 simulations, with assumptions regarding all other parameter distributions unchanged.
The mean risk of a clinical vCJD case per unit transfused for 2020 was estimated to be 1 in 1.5 billion if no UK residence deferral applied. This estimate was influenced primarily by risk from donors with prior residency in the United Kingdom (1 in 1.6 billion) compared to donors with travel-related history. No infections from transfusion were predicted for 2020 with or without a deferral. Over 99% of simulations estimated zero vCJD transmission risk (97.5th percentile equals zero), with the mean risk estimate driven by less than 1% of simulations generating rare cases.

Our risk estimates were sensitive to assumed current prevalence of UK primary exposure vCJD cases. We based analyses on an estimated 100 primary exposure cases (95% CI [11–220]) in the United Kingdom during or after 2020 according to Garske and Ghani, who predicted this number from 2010 onwards [6]. The Garske model estimated an annual case load increase from around 5 cases per year in 2011 to a peak in the period 2020–2030 at around 10 cases per year [6]. Given that there has been less than one case per year on average in the United Kingdom over that interval, and one case since 2014, this projection has substantially overestimated current risk [8].

In their vCJD transfusion risk modelling of transfused RBCs in the United States in 2011, Yang et al. [5] presented risk estimates using both a ‘low’ UK vCJD prevalence estimate based on the Garske model (100 asymptomatic undiagnosed cases in 2011, equivalent prevalence of 1.7/million) and a ‘high’ estimate derived from the rate of abnormal prion detection (493 cases per million) in surgically removed appendices in the UK [6, 24]. Yang et al. concluded that while the ‘low’ prevalence estimate provided reasonably accurate predictions for clinical cases of primary food-borne vCJD in the United States and transfusion-transmitted cases of vCJD in the United Kingdom and France, the use of the ‘high’ prevalence estimate led to much higher numbers than recognized at the time (2011) [5]. They concluded ‘predictions based on the low prevalence estimate are more consistent with clinical cases actually observed to date, implying that the risk, while highly uncertain, is likely very small’ [5]. In the intervening decade, no further cases of TT-vCJD have been recorded worldwide, and the results of a follow-up study (Appendix III) of the rate of abnormal prion protein in surgically removed appendices in the United Kingdom from before and after exposure to the BSE epizootic have been published [8, 25]. The latter study was intended as the ‘control’ for the two prior UK appendix studies (Appendices I and II) [23, 24], but the detection of positive appendices removed in both the pre-1980
and post-1996 cohorts (where no positive appendices were predicted because individuals were not 'exposed' to BSE contaminated products) complicated the interpretation of Appendices I and II results and, arguably, casts doubt on the original assumption that detection of abnormal prion protein in appendices correlates with pre-symptomatic vCJD [23–25] or a plausible infectivity estimate (refer to Data S2 for comprehensive discussion and analysis). The Appendix III investigators suggested two possible interpretations for their findings: (1) a low background prevalence of abnormal PrP in human lymphoid tissues that may not progress to vCJD or (2) all positive specimens are attributable to BSE exposure, a finding that would necessitate human exposure having begun in the late 1970s and continuing through the late 1990s [25]. Considering the conclusions of Yang et al. on the predictive accuracy of observed cases of vCJD and TT-vCJD using the ‘low’ and ‘high’ prevalence estimates, combined with the subsequently published results of the Appendix III study and the lack of additional cases of TT-vCJD despite more than 50 million transfusions in the United Kingdom since 2000, we consider it inappropriate to use the Appendix II data as a valid model parameter estimate for UK vCJD infectivity prevalence, and therefore use the ‘low’ (Garske-modelled) estimate as the basis for our risk estimates [5]. However, in the context of a sensitivity analysis, we did use the Appendix II-based estimate and confirmed the conclusions of Yang et al. that the predictions for vCJD cases and TT-vCJD cases in Australia to 2020 were incompatible with the (zero) observed cases (Tables S7 and S8) [5].

Our analysis took account of the potential for new peaks in vCJD risk associated with differing genotype-specific incubation periods, applying a mean incubation period for non-MM genotypes of 35 years as per Yang et al. [5]. Our resulting projections over the period 2020–2025 found continued declining transfusion risk in Australia under this assumption (Figure S2). In an importance analysis, non-MM incubation period was found to be an influential parameter in the model, after assumed prevalence levels and infectious dose per unit transfused. While it is possible that mean incubation periods for non-MM genotypes might exceed 35 years [33–35], the importance analysis showed only moderate change in potential future peak risk under this assumption. This predicted risk is reduced over time by decreases in numbers of at-risk donors as they reach the upper age of eligibility. Observed low case numbers may simply reflect that the susceptibility to vCJD in people with non-MM genotypes is well below the level assumed by Garske and Ghani [6].

In respect of infectivity per unit transfused, our modelling is based on the recent publication of updated ovine data by Salamat et al. [16]. This sheep transfusion model included sheep at all stages of the illness and therefore increased the risk, and suggests a transmission rate of 0.31 per unit in non-leucodepleted blood, with a 71% reduction to 0.09 with leucodepletion (0.01–0.14). This is also consistent with the updated UK-modelled risk assessment that used an infectivity per unit of 0%–20% [17].

There are some limitations to our analyses. We were not able to take account of the possible overlap between travel and prior-residency status in donors and therefore may have overestimated number of potential donors at risk who were categorized as both travellers and prior residents. However, the much stronger influence of prior residency as compared to travel on exposure risk means that any such adjustment is likely to have limited effect on estimates. A second issue is that projections of future vCJD transmission risk rely strongly on predicted future population growth, and predicted numbers of donors with prior UK residency, which in light of the ongoing COVID-19 pandemic are particularly uncertain in the post-2020 Australian environment.

Our modelled projections suggest that removal of the UK residence deferral would be a safe and effective strategy for increasing the donor base, as the potential risk is so small it can be considered essentially equivalent to the vCJD risk under the current deferral policy, while providing a substantial sufficiency benefit. The 2019 UK SHOT report reports a risk of death of 1 in 135,705 from overall transfusion-related adverse reactions [52]. Our estimate of 1 in 1.5 billion vCJD risk adds 0.01% to the baseline risk, which does not materially change the overall risk (1 in 135,690). However, there is a significant sufficiency gain, and we conservatively predict that the total donor number would increase by over 17,000 (57,000 donations annually) under this scenario, from the current population base of over 700,000 who are not eligible to donate in Australia because of the current deferral. [43].

Concluding, we predict a miniscule additional risk of vCJD transmission by transfusion in Australia if the current donor deferral for UK residence were to be ceased. Given that the predicted transmission risk without the deferral is magnitudes below that considered tolerable for blood safety in Australia and does not materially contribute to the total risk inherent in a blood transfusion, the Australian authors submitted to the Australian regulator a proposal to end this deferral and safely expand the donor base, which has now been approved. Our method may be useful to other blood operators wishing to reassess their vCJD transfusion risk exposure.

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CONFLICT OF INTEREST
The authors declare no competing financial interests.

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SUPPORTING INFORMATION
Additional supporting information may be found in the online version of the article at the publisher’s website.

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