Assessing the aggregated probability of entry of a novel prion disease agent into the United Kingdom

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Abstract

In 2018 prion disease was detected in camels at an abattoir in Algeria for the first time. The emergence of prion disease in this species made it prudent to assess the probability of entry of the pathogen into the United Kingdom (UK) from this region. Potentially contaminated products were identified as evidenced by other prion diseases. The aggregated probability of entry of the pathogen was estimated as very high and high for legal milk and cheese imports respectively and very high, high and high for illegal meat, milk and cheese products respectively. This aggregated probability represents a qualitative assessment of the probability of one or more entry events per year into the UK; it gives no indication of the number of entry events per year. The uncertainty associated with these estimates was high due to the unknown variation in prevalence of infection in camels and an uncertain number and type of illegal products entering the UK. Potential public health implications of this pathogen are unknown although there is currently no evidence of zoonotic transmission of prion diseases other than bovine spongiform encephalopathy to humans.

Keywords: Aggregated probability; entry assessment; prion agent

Introduction

Prion diseases, or transmissible spongiform encephalopathies (TSEs), are progressive neurodegenerative disorders that affect both humans and animals and are characterised by long incubation periods frequently of many years. Such disorders are biochemically characterised by conversion of a normal cellular form of the prion protein (PrP^{c}) into a misfolded disease associated form (PrP^{Sc}) that accumulates into amyloid protein aggregates in the brain [Norrby, 2011].

Scrapie in sheep was the first animal TSE to be described in the 18th century in Great Britain but TSEs have since been detected in a number of species, including scrapie in goats, chronic wasting disease (CWD) in deer and bovine spongiform encephalopathy (BSE) in cattle. The BSE crisis led to the slaughter of 3.3 million cattle and an estimated economic loss of £3.7 billion in the United Kingdom (UK) [Beck, 2007]. It is believed that BSE crossed the species barrier to humans through the consumption of contaminated beef and bovine products during the 1990s [ECDC, 2017] and that this zoonotic transmission of BSE has since led to the death of 178 people with variant Creutzfeldt-Jakob disease [NCJDRSU, 2019]. Prion diseases can therefore pose serious risks to both animal and human health and the first detection of a TSE in deer in Europe in 2016 demonstrates the continued need for a global awareness of these diseases [Benestad, 2016].

Within the European Union there is a statutory requirement to test for TSEs where disease is suspected and active surveillance systems to test for disease in healthy slaughter animals or fallen stock. However, in countries that do not have active surveillance systems, detection of cases relies on the reporting of clinical suspects where, if the animal keeper or veterinary surgeon are not familiar with the clinical signs, TSEs may not be considered in the differential diagnosis of neurological diseases or other conditions that present with similar signs [Konold, 2014]. Prion disease has recently been confirmed in three dromedary camels (*Camelus dromedarius*) from an Algerian slaughterhouse [Babelhadj, 2018] after clinical signs compatible with those of TSEs in other species were observed ante mortem. Disease associated pathological changes or prion protein were found in brain by Western blotting, histology, immunohistochemistry (IHC) and paraffin-embedded tissue blot; PrP^{Sc} was also detected in the lymph nodes of the one camel tested by IHC.

Information gathered from breeders and slaughterhouse personnel suggests that similar clinical signs had been observed since the 1980s [Babelhadj, 2018]. Subsequently, the disease has also been reported in a single case of a 12 year old dromedary camel from the region of Tataouine, Tunisia [Agrimi, 2019; OIE 2019].

There are many knowledge gaps about the biological characteristics of this new TSE, termed camel prion disease (CPD). Detection of infection in lymph nodes of one animal suggests extra-neural pathogenesis and, therefore, potential transmission of CPD between animals similar to that of classical scrapie and CWD. Such transmission of CPD could be facilitated over long distances by the traditional nomadic herding practices of dromedaries and the trade patterns between Algeria and other countries in North Africa and the Middle East [Bouslikhane, 2015]. In light of the devastation caused by BSE, and its subsequent zoonotic transmission, CPD was used here to assess the probability of entry of a novel prion disease agent into the UK via livestock and livestock products. The approach used was to assess the aggregated probability, using the number of imports per year to avoid potential under-estimation as has previously been described [Kelly, 2018]. Of note, the zoonotic potential of the disease is unknown and this assessment is of the probability of introduction of the CPD agent into the UK only, not of any onward transmission to humans or animals.

Methods

Risk Question and Pathway

The risk question to be addressed was:

'What is the aggregated probability of entry of the CPD agent into the United Kingdom from North Africa or the Middle East in one year?'

The risk pathway highlighting the probabilities to be considered for potential entry of the CPD agent into the UK is shown in Figure 1.

The approach used was qualitative and based on the framework set out by the OIE (World Organization for Animal Health) [OIE 2004]. The probabilities in Figure 1 are conditional and were expressed qualitatively as *negligible*, *very low*, *low*, *medium*, *high* and *very high* [EFSA, 2006; FAO, 2009]. The qualitative probabilities for each stage of the risk pathway up to, and including, the probability that an infected animal/animal product is not detected at import (*p1, p2, p3, p4, p5*) were combined as described previously [Gale, 2010] to give the probability of entry of an individual infected animal/product (*P*). Entry was defined as the probability of entry of a CPD positive animal or contaminated animal product into the UK within one year taking into account the current products which are imported from the regions of interest. For comparison, an aggregated probability of entry (*Pa*) of all categories of live animals/products was also assessed to provide an annual probability of entry using a graphical reference tool proposed by Kelly *et al.* [Kelly, 2018]. This tool removes some of the subjectivity that is often associated with deriving the annual qualitative probability of entry for animal import risk assessments as it enables the number of units imported to be combined with this individual qualitative event probability. In this way, the reference tool 'considers various qualitative categories of individual probability and determines the relationship between these probabilities, the number of imports and the annual probability of entry' [Kelly, 2018].

The quantitative bounds for the individual probability correspond to previously published example definitions [FAO, 2009] (Table 1).

Uncertainty associated with the estimates for the probabilities were categorised according to Spiegelhalter *et al.* [Spiegelhalter, 2011] depending on availability, completeness and quality of evidence.

Relevant data for use in the risk assessment were scarce. Briefly, the number of camel products imported into the UK from the area of interest was obtained from the EU Trade Control and Expert System (TRACES) where available. Otherwise, the following assumptions were made:

- The prevalence of CPD in camels in the region of interest - 3.1% (based on Bablehadj [Babelhadj, 2018])
- The incidence and prevalence of CPD in camel products, derived from:
    - Disease progression in camels – similar to scrapie (based on Bablehadj [Babelhadj, 2018])
    - Relative resistance of CPD associated PrP^{Sc} to heat and chemicals – similar to other TSEs (see Results section for references)
    - Correlation of disease presence and PrP^{Sc} deposition – similar to other TSEs (see Results section for references)
    - Systemic distribution of disease – similar to scrapie (based on Bablehadj [Babelhadj, 2018])
- The number of illegally imported products – based on data on illegal seizures and FAOSTAT production data
- The number of processed camel products both legally and illegally imported – assumed by the author

A further assumption made was that the aggregated probability calculations used the same quantitative bounds [FAO, 2009] as used in the tool by Kelly *et al*. [Kelly, 2018]. It is acknowledged that this probability could therefore change if these bounds were to be altered.

Results

Risk Assessment

Probability camel is infected with camel prion disease in exporting country (p1)

Detection of abnormal neurological signs since the 1980s within a restricted geographical area of Algeria suggests that the expansion of CPD to other areas (and countries) may be restricted or that the disease can remain largely undiagnosed. According to a recent presentation of the Mediterranean Animal Health Network, the disease was also reported in Tunisia and the incidence in the initial region of Algeria was described as 'rapidly and progressively increasing' [Agrimi, 2019]. It is, therefore, possible that movement of camels has allowed infected animals to enter other countries. Asides from the legal trade of camels, approximately 268 million people in Africa practice some form of pastoralism [Luizza, 2017]. For example, over 95% of cross-border trade within the Horn of Africa is unofficial and carried out by nomadic pastoralists trading livestock. Given that disease was first noticed in the 1980s and the nomadic way of life in this area, exporting countries were therefore considered as those making up the regions of North Africa and the Middle East for the purpose of this assessment.

Twenty of 937 camels in 2015 and 51 of 1,322 in 2016 showed neurologic signs at slaughter giving an overall estimated apparent prevalence of 3.1% in dromedaries brought for slaughter [Babelhadj, 2018]. In the absence of further information including confirmatory testing, an assumption was made that the prevalence of CPD in live camels in the regions of interest was *high* with *high* uncertainty because of the lack of testing data from countries other than Algeria and in only 3 camels in Algeria itself.

Probability infected animal is not detected on farm or at slaughter (p2)

Although anecdotal evidence suggests that herdsmen have noticed neurological signs in camels on the farm and at slaughter [Babelhadj, 2018] it was assumed that these animals were still being sent for slaughter and entering the food and feed chains. It was also assumed that as the other countries in the regions of interest have not been aware of the presence of this disease that they would not be surveying their animals for clinical signs and therefore animals will still be sent to slaughter. The probability of a camel with CPD not being detected on farm or at slaughter was therefore assumed to be *high* with *low* uncertainty.

Probability animal or animal product for export contains the CPD agent given the camel is infected and undetected (p3)

Camel products that can be legally exported to the UK, those for which databases exist to monitor the levels of exports and the probability of containing the CPD agent (given the source camel is infected) of these products are shown in Table 2.

The probability of a commodity containing the CPD agent depends on the presence of infectivity in the live animal and processes the commodity has undergone which may destroy it. As such, the uncertainty associated with this probability for all products was high as a result of knowledge gaps concerning these two factors.

The prion protein, PrP^{Sc}, has been shown to accumulate with infectivity and is therefore considered a reliable biochemical marker for infection [Thomzig, 2007]. PrP^{Sc} has been isolated from the muscle tissue, skin, milk and urine of TSE affected animals [Thomzig, 2007; Andréoletti, 2004; 2011; Chianini, 2015; Buschmann, 2005; Konold, 2013; Rubenstein, 2011; Henderson, 2015] and the pessimistic assumption here is that CPD distribution in a camel is similar to classical scrapie and CWD based on the detection of PrP^{Sc} in the lymphatic system [Bablehadj, 2018; Haley, 2014]. It was, therefore, estimated that the probability that a camel meat/milk/urine product contains the CPD agent, given it comes from an infected, undetected animal was *high*.

The only milk imported from the region of interest to the UK is Ultra-High temperature treated (UHT). This processing involves heating to ~135-145ºC for 1-10 seconds [Deeth, 2004] which is not sufficient to fully destroy prion activity [Yoshioka, 2013; Franscini, 2006]. Similarly for hides/skins, if they are not treated with a transformation process with a proven capacity to reduce TSE infectivity [SSC 2000], then it is considered unlikely that the CPD agent would be destroyed. The probability of UHT milk and hides/skins containing the CPD agent, was therefore estimated as *high*.

The European Food Safety Authority (EFSA) considered the risk of TSE transmission associated with semen and embryos collected from classical scrapie incubating sheep and goats to range from negligible to low [EFSA, 2010]. PrP^{Sc} in semen from a scrapie affected ram has been reported [Rubenstein, 2012] so the probability of semen from infected undetected camels containing the CPD agent was estimated to be *low* (worst case assumption based on the EFSA opinion). For hair PrP^{Sc} has been detected in the fibres of the follicular neural network and in the hair follicle isthmus in hamsters but not in the outer root sheet cells or the bulb region [Thomzig, 2007]. The probability of camel hair being infected with the CPD agent was therefore assumed to be *negligible* given the lack of evidence for PrP^{Sc} in the cells of the hair.

Soap products are described as containing ~ 25% raw camel milk and use a saponifying agent which starts the process of turning the raw ingredients into soap. This agent is usually 100% sodium hydroxide which is known to inactivate PrP^{Sc} at a concentration of 0.1M [Käsermann, 2003]. The probability of soap products and lip balm retaining the CPD agent was therefore estimated to be *negligible*. Chocolate products manufactured using camel milk can contain ~ 21% pure camel milk powder. Milk powder production involves spray drying milk in a flow of hot air between 180^{o}C to 220^{o}C [CWD 2019], sufficient to destroy prion activity [Somerville, 2011]. The probability of chocolate being infected with the CPD agent was thus estimated to be *negligible*. Camel milk does not curdle readily so camel cheese is traditionally consumed in fresh or fermented form. Fermentation is not expected to reduce the levels of infectivity so the probability of cheese from infected undetected animals being infected with the CPD agent was estimated to be *high*.

Products made from treated skins/hides from infected animals are assumed to have undergone a tanning process whereby the use of strong alkali and acid solutions will reduce the level of TSE infectivity [Käsermann, 2003; Appel, 2006; Hughson, 2016]. The probability of infection was therefore assumed to be *very low*. Similarly, although experimental evidence has demonstrated TSE infectivity in bone marrow [Huor, 2017; Seelig, 2010], during the process of cleaning bones for use in processed products such as jewellery it is assumed that the bone marrow is removed. The probability of camel bones being infected with the CPD agent, given an animal is infected, was therefore assumed to be *very low*.

Probability prion in live animal or animal product survives journey to the UK (p4) and is not detected at import (p5)

The probability of prions remaining infectious throughout the journey to the UK was assumed to be *high* with *low* uncertainty for all products for both legal and illegal routes due to the characteristic resistance of PrP^{Sc} to both chemical and physical degradation [Taylor, 1999] and evidence of its long term survival [Brown, 1991; Georgsson, 2006]. There are no gross lesions suggestive of TSE infection in animal products. There are also no post import tests for TSEs in either legal milk imports or illegal seizures. The probability of CPD infectivity not being detected on import to the UK was therefore assumed to be *high* with *low* uncertainty for all products for both legal and illegal routes. Additionally, the annual proportion of searched luggage among the total number of passengers entering a European country (Switzerland) has been estimated at between 0.06% and 0.24% [Jansen, 2016]. If this is applied to the UK then it suggests that the probability of an illegally imported infected animal product not being detected at import is *high*.

The probability of CPD not being detected in a live animal was considered to be *medium* as detection will depend on several factors including the animal showing clinical signs of TSE infection and the signs being correctly diagnosed as TSE by the veterinary inspector. The age of the animal and the progression of clinical disease will also be relevant. The uncertainty associated with this estimate was *low*.

Probability of entry of the CPD agent in an individual animal/product into the UK (P)

The probability of entry of the CPD agent in an individual animal/product into the UK was calculated by combining the probabilities in the risk pathway as described previously [Gale, 2010]. Results are summarised in Table 3 for both legal and illegal routes of entry for live animals and products.

Number of units imported into the UK per year (n)

Legal exports of live camels, camel meat (including untreated hides), urine and semen from the regions of interest to the UK are prohibited (Table 2). There were no imports of treated hides from camels from the region of interest recorded for the period 2010 to 2016 but, as such imports are permitted, the number of treated hides being exported to the UK was estimated to be within the range of 0 - 1. Since 2010 there has only been one possible consignment of ‘hair’ of species ‘other’ so may not have been of camel origin but an estimate of 1 unit was used here.

The Traces database has details of the volumes of milk and milk products imported into the UK. Approximately 10,830 kg of UHT milk products (it is assumed that the average product is 1 litre in size or 1 kg in weight giving a total of 10,830 units) and 11 Kg (equivalent to 22 units based on a 500g product) of cheese were exported to the UK in one year.

For processed products, soap, lip balm and milk chocolate made from camel milk are available in the UK via the internet or instore. Camel bone jewellery and ornaments and leather goods are also available for sale via the internet. It is assumed that these are all niche products with a limited market and the number of units of each product imported into the UK was estimated to be 1,000.

For illegal imports, data on illegal seizures were used to estimate the number of camel meat and dairy products illegally entering the UK. Illegal imports of red meat and dairy products are not categorised by species so, as a proxy for this, data (FAOSTAT) on the production of animals in the regions of interest were used to predict what percentage of each category would be a camel product. For 2016, camel meat contributed 4.7% to production of all red meat species and camel milk represented 0.47% of whole milk production (FAOSTAT) in the regions of interest. It is unknown whether the illegal milk/milk products seized would have undergone any heat treatment, but as stated above, UHT would not destroy infection. Using the illegal seizure data and FAOSTAT production data it was estimated that 242 units (200g products) of camel meat, 19 units (1Kg product) of milk and 20 units (500g product) of cheese illegally enter the UK in one year.

The number of illegal imports of treated skins/hides and hair was estimated to be between 0 -100 due to the size of the commodity and the low value placed on camel skins in the region of interest. The same figure was used for camel urine which has been used as a traditional medicine since ancient times [Abdel Gader, 2016] so it is possible that passengers entering the UK could illegally import camel urine for medicinal purposes.

For semen, there are difficulties associated with the application of artificial insemination in camelids in particular the collection and handling of semen due to the viscous nature of the seminal plasma [Skidmore, 2018]. Therefore the estimate for the number of illegal camel semen straws imported to the UK was between 1-10. The illegal import of batches of camel hair was also estimated to be between 1 - 10 due to the low value placed on camel hair in the region of interest.

The number of illegal imports of all processed products was estimated to be between 0 - 1000 assuming these are luxury products aimed at a niche export market.

Aggregated probability of entry of the CPD agent into the UK from North Africa or the Middle East per year (Pa)

The aggregated annual probability of entry of the CPD agent was estimated using the number of units of animals/products imported per year where known (or estimated by the authors where unknown) and the qualitatively assessed probability of entry for an individual infected product (Table 3) using the graphical framework described by Kelly *et al*. [Kelly, 2018].

For legal imports, the aggregated probability of entry was negligible for livestock, camel meat, urine and semen as these products are prohibited (Table 4). The probability was also negligible for hair, soap, lip balm and chocolate based on the assumed lack of infectivity in these products and the number of products imported. For cheese and UHT milk the probability of at least one infected unit entering the UK per year was high and very high respectively. The individual probability per unit for UHT milk increased from high to an aggregated probability of very high as a result of the number of units imported ($>10^4$) in one year.

The number of units per product illegally imported to the UK was estimated by the authors due to lack of data. This resulted in a range of probabilities for some products, from negligible if no items were imported to very high if 100 products were imported (treated hides/skins, urine) (Table 5). Milk products and cheese both had a high probability of entry and camel meat had a very high probability based on the estimated number of products imported.

Discussion

This assessment used the example of CPD to address the probability of entry of a novel prion agent into the UK. The estimated probability per unit was aggregated to take into account the number of units of each product imported per year. Thus the predicted probability is the probability of entry of one or more (i.e. at least one) infected unit per year into the UK. The predicted aggregated probability for legal imports was highest for UHT milk products and cheese whilst for treated hides and skins it was estimated to range from negligible to high depending on whether any units were imported in one year. For illegally imported meat, milk and cheese products the aggregated probability of at least one entry event per year was estimated as very high, high and high respectively. If testing were to be carried out to negate the presence of CPD in the camel population used to produce milk legally exported to the UK then the annual probability of entry would be reduced to negligible. Similarly, as the aggregated probability is based on an example of assumed quantitative bounds [FAO, 2009], were these bounds to be changed then the aggregated probability could also change.

The estimates of probability are associated with high uncertainty throughout the risk pathway hinging, in particular, on the application of a blanket prevalence of CPD within the camel population. The Middle East Respiratory syndrome coronavirus (MERS-CoV) provides an example of an undetected pathogen in camels which, once identified, has since been detected throughout much of the regions of interest suggesting that movement of camels has provided a route of incursion of the virus to different countries [Reusken *et al.*, 2013; Haagmans *et al.*, 2014; Meyer *et al.*, 2014; Reusken *et al.*, 2014]. It is possible that transmission of CPD between animals could have similarly been facilitated by movement of infected live animals although the disease has currently only been described in a restricted geographical area of Algeria and Tunisia. The involvement of lymphoid tissue, observed in both the Algeria and Tunisia cases, is suggestive of a peripheral pathogenesis, similar to scrapie and CWD in which horizontal transmission occurs efficiently under natural conditions [OIE 2019]. The uncertainty is compounded by lack of data on the epidemiology of CPD. As of June 2020, there is no publically available up-to-date information with regards to the prevalence of CPD in the area of interest or whether additional cases have been detected. The OIE Scientific Commission has called for the collection of further scientific evidence in countries with dromedary camel populations to measure the impact of the disease [OIE 2019]. This could influence the results of the risk assessment should an increase in the incidence of CPD have occurred.

The import of animal products in travellers' personal consignments presents a considerable risk of introducing infectious agents [Simons *et al.,* 2016; Hartnett *et al.,* 2007; Falk *et al.,* 2013]. Analysis from a study on illegal seizures of airline passengers in Germany, found that seizures are typically local foodstuffs reflecting culturally enrooted consumption patterns. Camel milk and meat are esteemed in the regions of interest for their medicinal properties; camel meat is also frequently eaten on special occasions or for ritual celebrations [Jansen *et al.*, 2014]. It is, therefore, not unreasonable to assume that a proportion of illegal seizures of milk products and red meat originate from camels.

Significant knowledge gaps exist about prion disease in camels. Although PrP^{Sc} is believed to be the most useful marker of TSE disease identified to date, it has also been shown that its presence does not always directly correlate with infectious titres and that bioassay is still required for verification of infection [Chianini *et al.*, 2015]. So far, this has not been reported for CPD. The relative heat resistance of camel prions is also unknown, a factor which could affect the risk pathway if it were proven to show a greater susceptibility to heat than BSE or scrapie prions. Disease progression in CPD could also affect the risk pathway, specifically the prevalence of infection in camel products, if the slaughter age of most camels is young and disease is only detected in older animals. Likewise, products from animals with CPD but not yet showing clinical signs could also contribute to the probability of entry; this is particularly important regarding the long incubation period of the prion diseases. Further research to gain a better understanding into the CPD agent behaviour and improvement of the market traceability of camel products may alter the probability estimates stated here and should be considered in future risk assessments.

In conclusion, this paper assesses the annual probability of at least one entry event of camel products containing the CPD agent into the UK. The probability of entry from the Middle East or North Africa was considered to be highest from legal import of milk and cheese and the illegal import of camel meat, milk and cheese. These estimates are associated with high uncertainty due to the number of assumptions made throughout the risk pathway in particular the prevalence of CPD in camels, and of the CPD agent in camel products, and the number of products illegally entering the UK. However, this assessment does not consider the consequence of the exposure of uninfected animal populations to these products, only the probability of entry of the agent. Therefore, whilst a high probability of entry of the CPD agent has been estimated for some products, whether there is a subsequent probability of onward transmission is unknown [Fryer 2011]. The zoonotic potential of CPD is unknown but there is currently no evidence of zoonotic transmission of TSEs other than BSE to humans. Further research to look at the zoonotic potential and risks to public health would be beneficial.

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Table 1: Definitions of the quantitative bounds used to correspond to the qualitative probability (taken from [*12*])

Qualitative level	Quantitative bounds	Quantitative bounds (%)
Negligible (N)	Indistinguishable from 0	Indistinguishable from 0%
Very Low (VL)	$<^{10-4}$, except 0	<0.01%, except 0%
Low (L)	10^{-3} to 10^{-4}	0.1% to 0.01%
Medium (M)	10^{-2} to 10^{-3}	1% to 0.1%
High (H)	10^{-1} to 10^{-2}	10% to 1%
Very High (VH)	$>10^{-1}$, not 1	>10%, not 100%
Certain	1	100%

Table 2: Probability of containing the CPD agent for individual commodities originating from camels including primary and processed products.

Commodity	Primary product used	Import to the UK allowed from regions of interest	Traceable (source)	Probability of containing the CPD agent (uncertainty in brackets)
Live animals				
Live camels	-	No	-	Certain
Primary products				
Meat	-	No	-	High (high)
Milk	-	Yes	Yes (Traces)	High (high)
Hair	-	Yes	Yes (Traces)	Negligible (high)
Urine	-	No	-	High (high)
Semen	-	No	-	Low (high)
Treated Hides and skins	-	Yes	Yes (Traces)	High (high)
Processed products				
Soap	Milk	Yes	No	Negligible (high)
Lip balm	Milk	Yes	No	Negligible (high)
Chocolate	Milk	Yes	No	Negligible (high)
Leather products	Skin	Yes	No	Very low (high)
Cheese	Milk	Yes	Yes (Traces)	High (high)
Bone ornaments	Bone	Yes	No	Very low (high)

Table 3: Probability of entry (*P*) of an infected camel or camel product for both legal and illegal pathways (uncertainty in brackets)

Probability	Livestock	Camel meat	UHT Milk products	Treated hides/skins	Urine	Semen	Hair	Soap and lip balm/Chocolate	Cheese	Bone/skin products
Camel Infected	High (High)	High (High)	High (High)	High (High)	High (High)	High (High)	High (High)	High (High)	High (High)	High (High)
Not detected	High (High)	High (High)	High (High)	High (High)	High (High)	High (High)	High (High)	High (High)	High (High)	High (High)
Animal or animal product (per unit) for export contains CPD agent	Certain (High)	High (High)	High (High)	High (High)	High (High)	Low (High)	Negligible (High)	Negligible (High)	High (High)	Very low (High)
Prion survives journey to UK	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)
Not detected on import	Medium (Low)	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)	High (Low)
Entry for individual infected product	Medium (Low)	High (High)	High (High)	High (High)	High (High)	Low (High)	Negligible (High)	Negligible (High)	High (High)	Very low (High)

Table 4: Aggregated probability of entry (*Pa*) of CPD infected animals/animal products via legal import with associated uncertainty in brackets using the method of Kelly *et al*. [9] *estimated by the authors

Legal	Livestock	Camel meat	UHT Milk products	Treated hides/skins	Urine	Semen	Hair	Soap and lip balm/Chocolate	Cheese	Bone/skin products
Entry for individual infected product	Medium (Low)	High (High)	High (High)	High (High)	High (High)	Low (High)	Negligible (High)	Negligible (High)	High (High)	Very low (High)
Number of units imported	0 (animals)	0 (200g product)	10830 (1 kg product)	0 – 1 (skins)	0 (500g product)	0 (straw)	1 (1 batch)	1,000* (item)	22 (500g product)	1,000* (items)
Aggregated probability of entry into the UK	Negligible (High)	Negligible (High)	Very high (High)	Negligible - High (High)	Negligible (High)	Negligible (High)	Negligible (High)	Negligible (High)	High (High)	Very low (High)

Table 5: Aggregated probability of entry (*Pa*) of CPD infected animals/animal products via illegal import with associated uncertainty in brackets using the method of Kelly *et al*. [9] *estimated by the authors

Illegal	Livestock	Camel meat	Milk products	Treated hides/skins	Urine	Semen	Hair	Soap and lip balm/Chocolat e	Cheese	Bone/skin products
Entry for individual infected product	Medium (Low)	High (High)	High (High)	High (High)	High (High)	Low (High)	Negligible (High)	Negligible (High)	High (High)	Very low (High)
Number of units imported	0-10* (animals)	242* (200g product)	19* (1 kg product)	0 – 100* (skins)	0 – 100* (500g product)	0 – 10* (straw)	0 – 10* (1 batch)	0 - 1,000* (item)	20* (500g product)	0 - 1,000* (items)
Aggregated probability of entry into the UK	Negligible - Medium (High)	Very high (High)	High (High)	Negligible – Very high (High)	Negligible - very high (High)	Negligible - Low (High)	Negligible (High)	Negligible (High)	High (High)	Negligible - Very low (High)

Figure legends

Figure 1: Risk pathway for the aggregated probability of entry of the CPD agent into the UK in one year