Temporospatial distribution and country of origin of canine transmissible venereal tumour in the United Kingdom

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Abstract

Objective

Transmissable venereal tumour (TVT) is a tumour transplanted by physical contact between dogs. Lesions typically affect the genitalia. TVT is not considered enzootic in the United Kingdom (UK), with cases seen in imported dogs. We sought to determine the patient characteristics, temporal and spatial distribution, and country of origin of affected dogs in the UK.

Methods

Electronic pathology records (EPRs) from four UK veterinary diagnostic laboratories collected between 2010 and 2019 were searched for the terms 'venereal' or 'TVT'. Reports were reviewed for statements confirming a TVT and descriptive statistics collated.

Results

Of 182 EPRs matching the search terms, a diagnosis of TVT was confirmed in 71. Country of origin was noted in 36 cases (50.7%) with Romania being the most common (n=29). Cases were reported in each UK constituent country, with the majority being in England (64, 90.1%). The incidence of TVT diagnosis increased over the last decade ($z=2.78$, $P=0.005$).

Conclusions/Discussion

The incidence of TVT diagnosed in the UK is increasing. The majority of cases were known to have been imported. Autochthonous transmission cannot be excluded due to study design. Vets are encouraged to carefully examine the genitalia of dogs imported to the UK from countries with enzootic TVT.

Introduction

Canine transmissible venereal tumour (TVT) is an infectious tumour of dogs (1–4). TVT is transmitted between dogs by direct transplantation of living tumour cells from one dog to another, typically during

mating when abraded mucosa is exposed to the tumour of an infected dog (4). Transmission via licking, sniffing and parturition have also been reported, thus TVT represents an infectious cell line that is transmissible as a naturally occurring allograft (4–7).

TVT is the oldest and most widely disseminated cancer in the natural world, with evidence of emergence approximately 11,000 years ago (8,9). TVT can be transmitted only via living tumour cells – not killed cells or cellular filtrates. This demonstrates the transmissible nature of the cells themselves (4,6,10). The patterns of genetic identity found in tumours located in different continents is consistent with a single clonal origin (6,8). Normal canine cells have 78 chromosomes while TVT cells have a vastly rearranged karyotype containing 58-59 chromosomes (11,12). Though TVT is classified as a round cell tumour hypothesised as being of histiocytic origin (13,14), its original cell of origin is not definitively known.

Lesions typically affect the external genitalia of dogs of either sex but can also be present in other locations such as cutaneous, nasal or oral lesions (15–17). The tumour can range in size from a small nodule to a large mass and is typically cauliflower-like, firm but friable and frequently ulcerated or inflamed. Local invasion is common, but distant metastasis is rare and usually only occurs in immunocompromised dogs or puppies (5).

As an allograft, TVT should be readily cleared by an immunocompetent host, as occurs in organ transplant without immunosuppression. When an immunocompetent, naïve adult dog is exposed to an infectious transplant of TVT cells, a tumour growth phase of 2-6 months occurs. During this period, very low levels of major histocompatibility complex (MHC) expression likely contribute to the tumour's ability to evade immune surveillance (18–21). After the growth period, whilst some TVTs stabilise in size, most regress. The factors that lead to the initial implantation of the tumour and the switch between the growth and stabilisation/regression phases are incompletely understood, but the latter phase is associated with increased tumour MHC expression, and a parallel increased immune response against the tumour (18–21). These changes in MHC expression are hypothesised to be the most significant contributor to the tumour's natural history, and as a consequence, TVT is rarely fatal, but is perpetuated within the population by tumour transmission during the period of immune evasion (6).

Whilst spontaneous regression has been reported in experimental settings (22) the course of naturally acquired TVT is not well documented and therefore it should not be assumed that spontaneous regression will occur. Consequently, to ensure resolution, reduce associated welfare issues and prevent further transmission most cases in pet animals are treated. Weekly systemic treatments with vincristine are most commonly used, and typically lead to regression and clinical cure in 3-5 weeks (23–26). Radiotherapy has also been used in refractory cases, with good responses reported (27).

Worldwide, TVT is a common disease and has been reported in all inhabited continents (28,29). It is typically associated with stray or free roaming dog populations in which uncontrolled mating occurs

(28). TVT is more common in tropical and sub-tropical regions and is uncommon in North America and North and Central Europe, largely due to control of stray dog populations (28). In the United Kingdom (UK), TVT is not considered enzootic, but occasional cases have been anecdotally reported in imported dogs.

A huge amount of epidemiological information is held within the pathology records of diagnostic laboratories pertaining to signalment and diagnosis of neoplasia. They are one of the possible sources of information for tumour registries. Tumour registries are important tools in the epidemiological monitoring of cancer; they have been used to assess and monitor incidence of cancer and determine effectiveness of public health interventions in reducing cancer rates (30,31). The Small Animal Veterinary Surveillance Network (SAVSNET) collects both patient clinical records from veterinary practices and EPRs from diagnostic laboratories, using them for a variety of purposes including monitoring for infectious diseases (32,33) and surveillance (34). The diagnostic laboratory data includes EPRs from the majority of the UK's commercial diagnostic laboratories and therefore represents a rich and novel source of information for evaluating the occurrence of TVT in the UK setting.

Given the lack of knowledge of TVT within the UK, and the (albeit small) potential for this condition to become established and endemic in the UK from dogs imported or returning from overseas, the aim of this study was to describe TVT cases diagnosed in the UK including the incidence, neuter status, geospatial distribution and country of origin of affected dogs.

Materials and Methods

This is a retrospective cohort study. The dataset was developed by searching datasets of cytology and histopathology submissions made to four comercial laboratories in the UK between the 29th September 2010 and 30th October 2019 (inclusive). This data had been collated anonymously as part of the laboratories' voluntary participation in SAVSNET, which has been ethically approved by the University of Liverpool research ethics committee (RETH0000964).

In order to identify possible cases, a digital search term was developed using the phrases 'venereal' or 'TVT'. The EPRs identifed were manually evaluated by a single domain expert (DG). The inclusion criteria were dogs who had been diagnosed with TVT on the basis of a cytology and/or histology sample. Cases were excluded if the report was about any other species aside from dogs, the results did not pertain to a histology or cytology sample, a diagnosis other than TVT was reached or the pathologist suspected TVT, but suggested further diagnostic tests such as immunohistochemistry were required to confirm the diagnosis, and there was no recorded evidence from the EPR that these were performed.

Patient data was collated for cases, including signalment (age, breed, sex, neuter status) when available, date of submission (this date was chosen over date of diagnosis as the latter was not always available), lesion location, whether cytology, histology or both were performed, geographic location. Information pertaining to travel status or country of origin (if recorded) were also included.

Data was exported to a Microsoft Excel spreadsheet, cleaned by harmonising variable terms (eg dog and canine), duplicates removed using the laboratory sample accession number (e.g. dogs that had two submissions under an identical lab number typically if there was both a cytology and histology sample), and descriptive statistics performed. A Mann-Kendall trend test was performed using the 'trend' package in R (version 4.0.3) to assess incidence of TVT cases over time per 10,000 cytology or histology submissions submitted for any clinical reason, over the aforementioned time period. A map documenting diagnoses of TVT during the study period by UK administrative area was created using the Microsoft Excel for Mac (Version 16.45) 'Filled Map' chart. A Mann-Kendall trend test was performed to address the possibility that increasing case numbers may be an artefact caused by an overall increasing number of laboratory submissions or the increasing market share of the participating laboratories. The yearly incidence of TVT cases per 10,000 (with 95% confidence intervals) cytology or histology submissions to laboratories over the same time period was assessed. 95% confidence intervals surrounding annual proportional incidence in TVT diagnosis compared to all histological and cytological submissions being submitted for that year were calculated using the exact interval method (also known as the Clopper-Pearson interval) available via the 'prevalence' R package(35). A p value of <0.05 was considered significant.

Results

The initial case population comprised 182 cases, comprising 81 cytology and 101 histology samples. Of these, 45 reports were excluded because although the pathology was consistent with a round cell tumour, the exact diagnosis as recorded in the EPR was not definitive. In these reports, further testing had often been recommended without recorded linked evidence of it being performed, or a final diagnosis was not reached. A further 56 reports were excluded as they were diagnosed with another condition (Supplementary table 1), and 10 were excluded as the samples were non-diagnostic.

Seventy-one cases met the inclusion criteria, of which 13 were diagnosed by cytology (18%) and 58 (81%) by histology. Only 5 included cases had both a cytology and histology submission and there were no cases where these results were contradictory. The majority of affected dogs were mixed breed (n=47, 66%). Other breeds represented included Border Collie (n=2), Staffordshire bull terrier (n=2), Labrador retreiver (n=1) golden retreiver (n=1), Chihuahua (n=1), English setter (n=1), Newfoundland (n=1) and old English sheepdog (n=1). The breed of 14 dogs was not recorded. Twenty-five (35%) were female neutered, 27 (38%) male neutered, eight (11%) were entire male, and eight (11%) were entire female.Sex was unknown in three dogs. Age data was not present for a lot of records which precluded meaningful analysis.

The described lesions were predominantly assocated with the genitalia. In the 33 female dogs, 23 (69.7%) were reported as affecting the vagina, and seven (21.2%) the vulva. In the 35 male dogs, 18 (51.4%) were located on the penis and 14 (40.0%) on the prepuce. The majority of lesions were on the genitalia regardless of neuter status. Other less common locations included lip, the perineum and a lymph node (one case each). Lesion location was not recorded in six cases. The majority of cases

(47/71, 66%) presented with a single lesion. Multiple lesions were reported in 8 cases (11%) including the case where TVT was diagnosed in the lymph node. The history from the submitting vet in that case described ‘multiple skin lesions’ but these were not sampled. It would be suspected that at least some of those lesions were TVT as a primary lymph node TVT would be extremely unusual. Number of lesions was not reported in 16 cases (22%). As this data was obtained from the pathology submission form (rather than direct examination of the animal) the possibility that some cases classified as having a single lesion actually had multiple lesions cannot be entirely excluded.

Import status and country of origin was reported in 36 of the 71 cases (50.7%), of which the majority were reported to be from Romania (29 of 36, 81.0%). Other countries of origin included Serbia (2), Spain (1), China (1), Greece (1) and Gambia (1). One further dog was listed as imported, but a country of origin was not stated.

Within the UK, based on the postcode of the submitting veterinary practice, the majority of cases were seen in England (65 of 71, 91.5%). Four cases were reported from Scotland and one each from Northern Ireland and Wales. The location of one submitting practice was unknown. Cases were seen across England (Figure 1), although the highest proportion were in the south, with 26 of 71 in the South East, and seven in the South West region. Twelve were located in the East Midlands and three in the West Midlands. Six cases were seen in the East of England and three in Yorkshire and the Humber. In the north of England, six cases were seen in the North West region whereas one was seen in the North East.

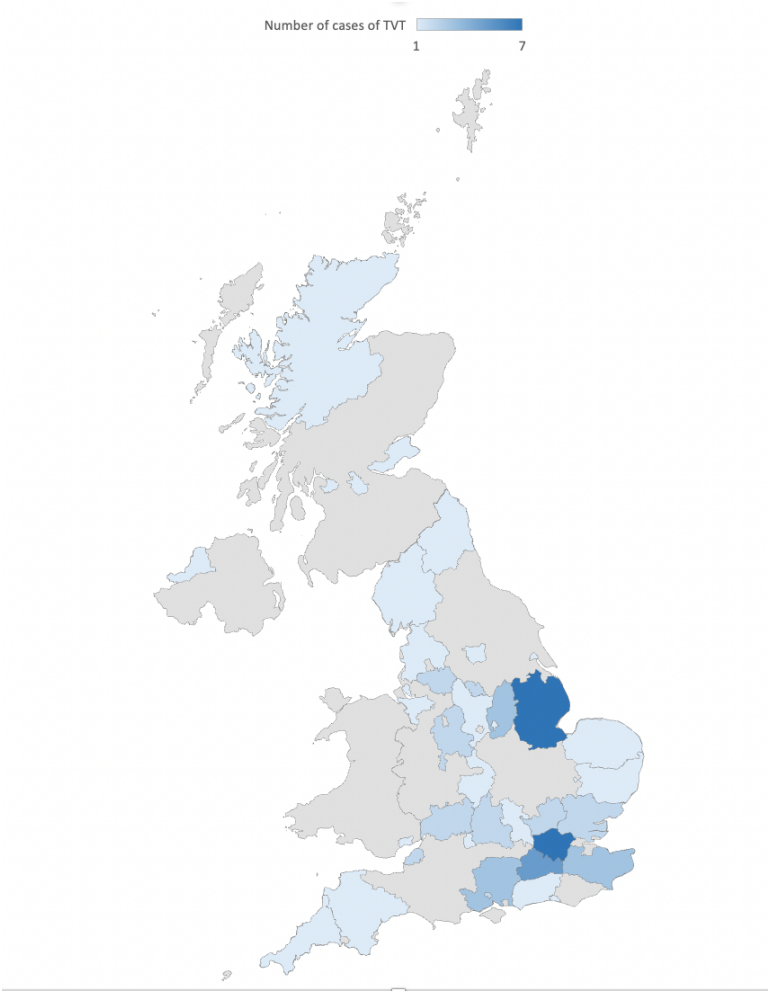

Figure 1: Veterinary practice site distribution of TVT cases across the UK. Deeper shades of blue indicates more cases. Grey areas had no recorded cases. There may be some bias in this figure from underlying population size and laboratory demographics

While the total number of cases remained low, the frequency with which TVT was diagnosed increased over time (Figure 2), with very few cases seen prior to 2014 and the numbers increasing steadily thereafter.

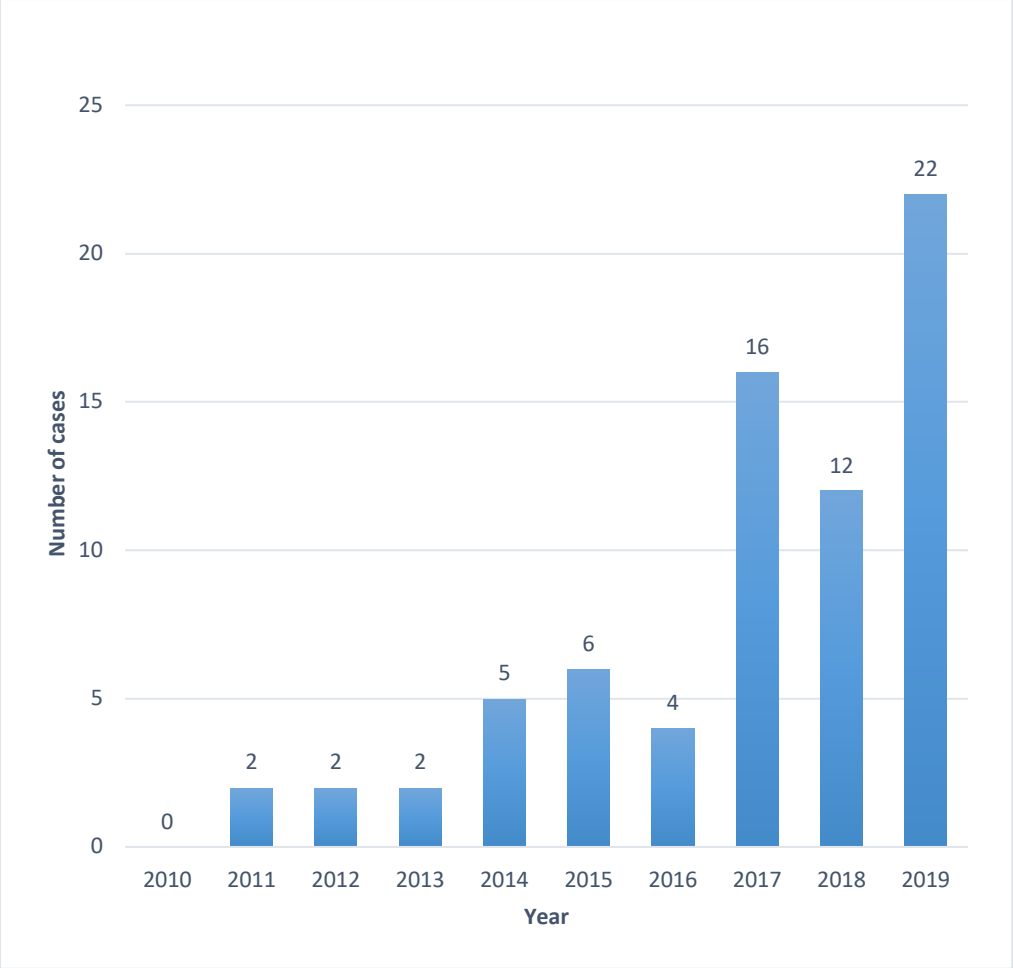

Figure 2: Number of TVT diagnoses by year across the participating UK laboratories

The Mann-Kendall trend test was was performed to assess the rate of TVT cases per 10,000 (with 95% confidence intervals) cytology or histology submissions to laboratories over the same time period (Figure 3). This showed a significant upward trend ($z=2.78$, $P=0.005$), which is consistent with an increasing incidence of TVT cases.

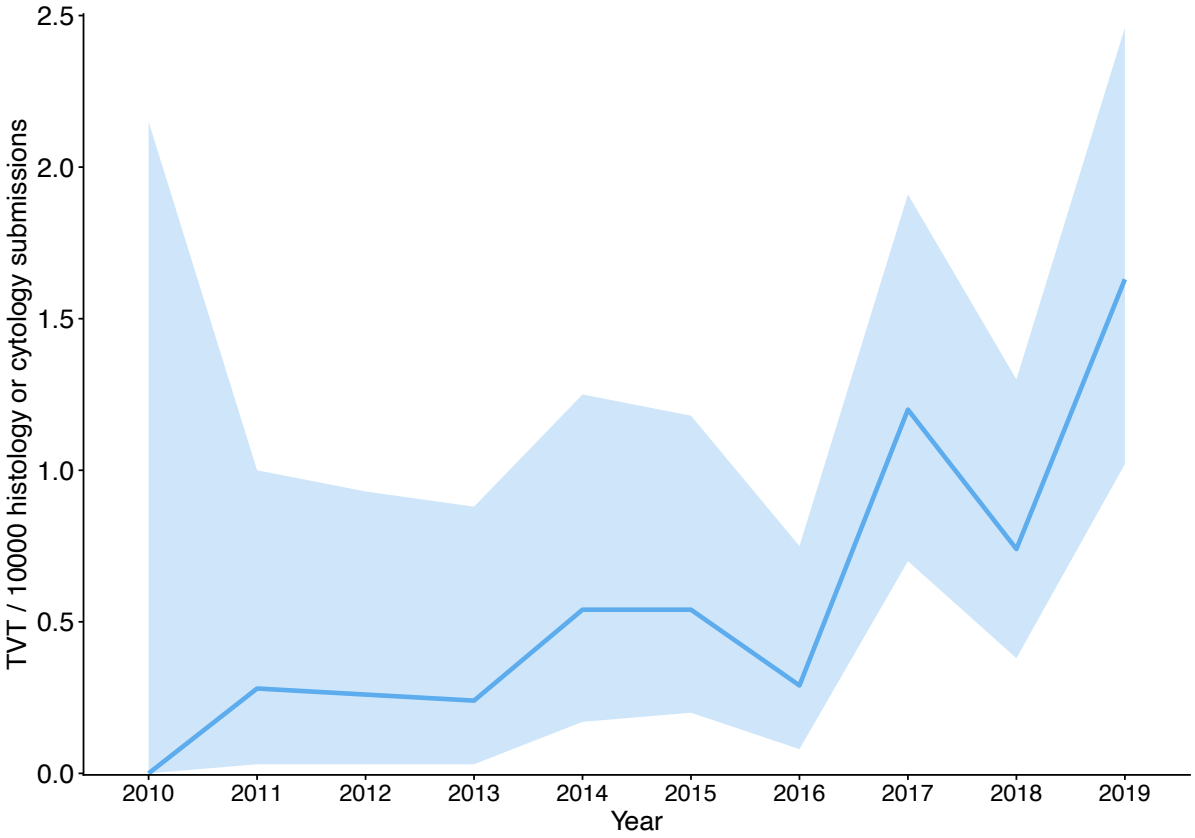

Figure 3: Yearly incidence of TVT diagnosis per 10 000 cytology and histology submissions (blue line) with 95% confidence intervals (blue shading)

Discussion

TVT is an unusual infectious tumour of dogs that is transmitted by physical transplantation. TVT is primarily transmitted during mating activity. There are various historical reports of TVT presence within the UK, but it is not believed to be enzootic in the UK currently probably due to the high rates of elective neutering and low numbers of stray or feral dogs (4,28,36). The co-occurrence of large populations of free-roaming dogs, lower GDP per capita and warmer conditions in countries with higher TVT prevalence means that it is not possible to draw a certain conclusion on the impact of climatic conditions on its spread (4,28). This study showed that while TVT is still rare in the UK, the incidence of diagnosis has risen over the period studied. Within the UK, the majority of cases were seen in England although this may reflect selection bias as the included laboratories were located in England. It also likely reflects that England has both a higher human population, and with it a higher dog population (37).

As would be expected with TVT the majority of lesions in this study were located on the genitalia. As this study was conducted with laboratory data rather than the associated clinical record it is impossible to know if these were the only lesions present or if multiple were present but only one sampled. This is particularly relevant with the case of TVT identified in the lymph node. Having no associated genitalia, facial or other lesion would be very unusual. It is suspected that this case did indeed have another

lesion and the lymph node represents metastasis but unfortunately we had no records of another lesion being sampled in this case.

The majority of cases in this study affected dogs that were reported to have been imported. It is easy to speculate that most or all of the remaining dogs were also imported. However, in the context of determining origin, a limitation of this study is that it relies on information both being included on the submission form and then also being transposed into the EPR by the pathologist. Consequently, this data cannot absolutely exclude local presence and transmission. Ensuring that the import status and country of origin of the patient are included in the medical record and on laboratory request forms would facilitate epidemiological monitoring of this and other diseases considered non-enzootic and would allow identification of possible local spread with more confidence.

In recent years it has become increasingly popular for UK residents to adopt a dog from a foreign rescue organisation rather than buy or adopt a dog locally in the UK (38). It has recently been reported that the majority of these rescue dogs are being imported incorrectly under the European Union Pet Travel Scheme (PETS; EU regulation 576/2013), which is for the non-commercial movement of animals accompanied by their owners (38). Dogs imported for commercial reasons including for a change of ownership (sale of puppies or rehoming rescue animals) are covered by the more stringent Balai directive (EU regulation 92/65/ECC) (38). The consequence of this approach is that rehomed pets may not necessarily have undergone the pre-export health check required by the Balai directive, and the opportunity to identify TVT prior to entry into the UK may have been missed.

In the context of the disconnect between import legislation and the facts on the ground it is interesting to observe that the incidence of TVT cases has increased in the UK over the past decade. Of the dogs with a country of origin noted in the EPR, 80% came from Romania. TVT is known to be enzootic in Romania with a prevalence estimate of 5 – 10% in a recent study due to a large roaming dog population and low rates of neutering (29). Animal & Plant Health Agency (APHA) figures show 39,998 dogs were imported into the UK from overseas under the Balai directive in 2017 (39), with 15,556 (38%) of these originating from Romania (40). There has been an increase in dogs imported from Romania over recent years; according to APHA no Romanian dogs were imported into the UK in 2013 (41) while 15,556 were imported in 2017 (40). This makes Romania now the most common origin for imported dogs. The high number of cases from Romania therefore represents a combination of high prevalence and high import rates. Cases imported from other locations with high prevalence likely carry a similar risk of importing TVT on a per imported dog basis. In 2017, 287,016 dogs were imported into the UK under PETS (39). As the Animal & Plant Health Agency does not record the country of origin for dogs entering under PETS (42) and the Balai directive is not always being used as intended, the number of puppies and rescue dogs imported into the UK cannot be fully known. This leaves a weakness in the UK's capability to monitor and exclude non-enzootic disease.

The drivers behind the increasing population of dog importation into the UK are likely a combination of the relaxation of the PETS travel scheme requirements in 2012 (43), and the passing of a law in Romania in 2013 which enables stray dogs to be euthanised if not claimed within 2 weeks (38). This led to the formation of several charities in the UK, mostly formed during or after 2014 in response to the above law. With the increasing number of dogs being imported (38,40–42), it could be expected that some of the risk of import of non-enzootic diseases such as TVT has increased, and this has led to growing concern in the veterinary community about the possibility of introduction non-enzootic diseases (38,44–51). This is particularly true since the PETS travel scheme was changed in recent years to make tick treatment non-mandatory. This step increased the risk that foreign ticks and associated vector-borne diseases could become established in the UK. Indeed, in recent years, cases of leishmania, babesia, and *Hepatozoon canis* infection have been reported in rehomed imported dogs, and in some cases local transmission has been confirmed (46,50,52–55). Given the natural variation in exposure risk to particular infectious diseases in different countries it may be prudent to vary monitoring and entry requirements dependent upon local risk.

The importation of non-enzootic parasites and diseases has also been seen in multiple other countries including (but not limited to) the importation and establishment of *Dirofilaria repens* (56) and more recently *Dirofilaria immitis* (56,57) into Austria, the importation of leishmaniasis into Canada (58) and several non-enzootic (typically northern) European countries (59). Whilst there is no current data on TVT being imported into other non-enzootic countries in a similar way, it is certainly possible and careful examination of imported dogs is encouraged.

Interestingly the majority of dogs in this study were recorded as neutered. As TVT is largely transmitted through coitus (4) and almost all of the lesions were documented to be on the genitalia it seems probable that most of these dogs were entire at the time of transmission and neutered shortly before or after arrival into the UK. The risk of chains of local transmission in the UK is considered low both because most imported dogs are neutered at the time of import or very soon thereafter (38) and because the neutering rate in the UK is high reducing the number of local dogs that might engage in mating activity. However, local spread cannot be completely excluded as almost a quarter of dogs were recorded as entire at time of diagnosis.

This study represents an innovative use of an EPR tumour registry to monitor the changing incidence of an unusual canine cancer over a number of years. One consideration when using such data is that the diagnostic criteria may change over time. In this context it is worth noting that the proportion of cases in which TVT was mentioned, but in which a final diagnosis of TVT was not made broadly tracked the total number of recorded cases each year. Consequently, a change in a pathologist's willingness or ability to diagnose TVT is unlikely to explain the increase seen.

The nature of laboratory data means that no information about timing of neutering relative to importation, interval between import and presentation to a veterinary surgeon (each of which influence the potential

for TVT to spread locally), treatment or outcome was present. As SAVSNET does have access to a large amount of primary practice data, there is an opportunity to examine these questions in a future study.

This study had several limitations. It was retrospective and EPR data has particular limitations. It is likely that the incidence numbers in this study are an underestimate, as a reasonable number of cases had to be excluded due to a lack of a definitive diagnosis and unfortunately, due to the elapsed time the histology blocks were not available for review. Moreover, these pathology reports do not cover all submissions made by UK veterinarians. Further, due to the possibility of spontaneous remission we cannot be sure that all tumours will have been sampled and not all of those sampled will be submitted for pathological assessment.

As the Mann-Kendall test is aimed at identifying presence of monotonic trends, it is not well suited to account for seasonal variation in incidence. As we have approached analyses on an annual basis here, we do not anticipate this to have impacted our findings, however. We have summarised findings from multiple diagnostic laboratories here, though due to the low number of cases observed we have not attempted to account for potential clustering effects between laboratories. We therefore cannot completely exclude the possibility that variation in diagnostic approach between laboratories might have impacted on findings as a result.

There may also be bias in this study as a significant number of cases needed to be excluded due to a lack of a definitive diagnosis of TVT (in these cases the diagnosis was most commonly 'round cell tumour'). It is possible that pathologists were less likely to definitively diagnose TVT in non-genital lesions, particularly if no travel history was reported by the referring vet.

This study shows that databases of EPRs such as those curated by SAVSNET have significant potential as a disease and cancer surveillance tool and therefore represent a useful addition to the veterinary cancer surveillance initiatives already in place or being developed (60–62). In this study we identified that the incidence of TVT diagnosis is increasing in the UK and it appears to be linked to dog importation especially from Romania. Based on these data, veterinary surgeons should carefully examine the genitalia of all imported dogs at initial assessment and encourage neutering of these patients either prior to entering the country or immediately thereafter to reduce the risk of local spread. Moreover, as local transmission cannot be completely excluded, TVT should be on the differential list for any canine genital masses identified in the UK.

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Supplementary Table 1: common non-TVT diagnoses of excluded cases

Diagnosis	Number of cases
mast cell tumour	6
plasmacytoma	12
inflammation	11
lymphoma	4
histiocytoma	8
seminoma	4
Plasmacytoma/histiocytoma	7