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Global meta-analysis of over 50 years of multidisciplinary and international collaborations on transmissible cancers

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Abstract

Although transmissible cancers have, so far, only been documented in three independent animal groups, they not only impact animals that have high economic, environmental and social significance, but they are also one of the most virulent parasitic life forms. Currently known transmissible cancers traverse terrestrial and marine environments, and are predicted to be more widely distributed across animal groups; thus, the implementation of effective collaborative scientific networks is important for combating existing and emerging forms. Here, we quantify how collaborative effort on the three known transmissible cancers has advanced through the formation of collaborative networks among institutions and disciplines. These three cancers occur in bivalves (invertebrates—disseminated neoplasia; DN), Tasmanian devils (vertebrate—marsupial; devil facial tumour disease; DFTD) and dogs (vertebrate—eutherian mammal; canine transmissible venereal tumour; CTVT). Research on CTVT and DN has been conducted since 1876 and 1969, respectively, whereas systematic research on DFTD only started in 2006. Yet, collaborative effort on all three diseases is global, encompassing six major Scopus subject areas. Collaborations steadily increased between 1963 and 2006 for CTVT and DN, with similar acceleration for all three cancers since 2006. Network analyses demonstrated that scientists are organizing themselves into efficient collaborative networks; however, these networks appear to be far stronger for DFTD and DN, possibly due to the recent detection of new strains adding impetus to research and associated publications (enhancing citation trajectories). In particular, global and multidisciplinary collaborations formed almost immediately after DFTD research was initiated, leading to similar research effort and relatively greater research outputs compared to the other two diseases. Therefore, in the event of outbreaks of new lineages of existing transmissible cancers, or the discovery of new transmissible cancers in the future, the rapid formation of international collaborations spanning relevant disciplines is vital for the efficient management of these diseases.

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KEYWORDS
data-mining, emerging diseases, meta-analysis, outbreak, quantitative review, research impact

1 | INTRODUCTION

Collaborations allow scientific questions to be answered efficiently, facilitating innovative advances in scientific knowledge (e.g. Årdal et al., 2016; Deeks et al., 2016; Sutherland et al., 2013). A collaboration is defined as two or more scientists from the same or a different institutions that compile a paper together (Newman, 2001). Examples of ground-breaking developments through large-scale, international collaborations in the field of science include the discovery of the Higgs Boson, an elementary particle in the Standard Model of particle physics theorized in the 1960s (ATLAS Collaboration, 2012), the mapping of the human epigenome, the chemical compounds and proteins that attach to DNA and switch genes on and off (Stunnenberg et al., 2016), and the NASA Twins Study investigating how the human body adapt to and recover from long-term exposure to the extreme environment of space (Garrett-Bakelman et al., 2019). The benefits of such international collaborations have been investigated by a range of scientific fields, including conservation (Kark et al., 2015; Mazor, Possingham, & Kark, 2013), ecology (Goring et al., 2014; Leimu & Koricheva, 2005) and medicine (Årdal et al., 2016; Deeks et al., 2016). These studies have highlighted the importance of obtaining key insights into complex systems, particularly with respect to cancers in humans (The International Cancer Genome Consortium, 2010) and infectious diseases (Årdal et al., 2016; Deeks et al., 2016). Without doubt, deciphering complex biological scenarios requires strong collaborations between multidisciplinary groups (often at an international scale).

Cancer is one such complex system that has been described in most of the main groups of multicellular organisms, including plants and invertebrates (Albuquerque, Drummond do Val, Doherty, & de Magalhães, 2018). Most cancers are nontransmissible, forming clonal cell lines that tend to cause the death of the host and the cancer to disappear. Yet, some cancer cell lines exist that are able to infect new hosts (termed horizontal transmission). Such transmissible cancers have, so far, only been detected in a few vertebrate and invertebrate groups, namely bivalves (invertebrates—disseminated neoplasia; DN), Tasmanian devils (vertebrate—marsupial; devil facial tumour disease; DFTD) and dogs (vertebrate—eutherian mammal; canine transmissible venereal tumour; CTVT) (Metzger et al., 2016; Murgia, Pritchard, Kim, Fassati, & Weiss, 2006; Pearse & Swift, 2006, see Table 1 for an overview). While transmissible cancers seem rare, the recent discovery of two transmissible cancers in Tasmanian devils (DFT1 in 1996, Hawkins et al., 2006; Pearse & Swift, 2006; and DFT2 in 2016 Pye et al., 2016), as well as a new lineage of DN in two new bivalve species (increasing the number of DN lineages to 6, Yonemitsu et al., 2019), present the question of whether transmissible cancers are more common than previously thought (Metzger et al., 2016; Ujvari, Gatenby, & Thomas, 2016b).

Several environmental, host and cell factors must converge (e.g. survival during transit, a permissive host environment and the propagule pressure which is the number of times and the frequency a host is exposed to a potential infection) for the emergence and persistence of transmissible clonal cell lines (see the "perfect storm theory" Ujvari et al., 2016a), with contagious cancers likely having evolved and gone extinct over evolutionary time. Once the neoplastic process has crossed the threshold of contagiousness, malignant cells become new parasitic "species," and their ecological consequences can be major (e.g.> 85% population decline in 20 years in Tasmanian devils; epizootic outbreaks and mass population declines in marine mollusc populations, Mateo, MacCallum, & Davidson, 2016), making these cancers one of the most virulent parasitic life forms. Contagious cancers have likely evolved and gone extinct over evolutionary time in various species. However, due to our limited ability to detect transmissible cancers across evolutionary timescales, it is currently not possible to determine how common they were in the past, their current prevalence or potential prevalence in the future (Thomas et al., 2017).

Such complex systems require the construction of efficient collaborative networks across institutions and disciplines. It is, therefore, important to establish the optimal structuring of efficient networks. While knowledge about CTVT has built over a 150-year timeframe (Novinsk, 1876), DFTD has only been studied for about 13 years (from 2006, Pearse & Swift, 2006). These different timeframes provide a unique opportunity to investigate how scientists have organized themselves in collaborative networks to obtain insights of these cancers, and to delineate how groups should organize themselves in the event of a new transmissible cancer emerging. Thus, here, we conducted a meta-analysis of the currently known three transmissible diseases, using bibliometric and social network analyses to quantify: (1) how collaborations are organized, (2) how the organization of these networks has changed over time and (3) the efficiency of information sharing in these networks. We applied our results to suggest how future collaborations should be optimally structured to respond to outbreaks of new lineages of existing transmissible cancers, or the discovery of new transmissible cancers in the future, which could also be applied to scientists working on other infectious diseases.

2 | MATERIALS AND METHODS

2.1 | Selection of studies for the meta-analysis

Following the protocol of Dujon and Schofield (2019) and Dujon (2019), for each of the three transmissible cancer types we searched the Thomson Reuters ISI Web of Science™ database, the Scopus

TABLE 1 Summary of the main characteristics of transmissible cancer in wildlife

	Canine venereal tumour disease (CTVT)	Devil facial tumour disease (DFT1 and DFT2)	Disseminated neoplasia (six lineages)
Species affected	Dogs (coyotes, jackals can be infected artificially)	Tasmanian devil (*Sarcophilus harrisii*)	Clams, mussels, cockles and oysters
Appeared	>10,000 years ago	>20 years ago for DTF1 and > 5 years for DFT2	>50 years ago
Year it was demonstrated to be transmissible	1876	2006	2015
Distribution	Worldwide	Tasmania (Australia)	Worldwide
Cell of origin	Myeloid cells	Schwann cells or precursors	Haemocytes
Permissive environment	Low genetic diversity of host species	Low genetic diversity of host species	Potential environmental stress
Spreads via	Sexual intercourse and licking of affected areas	Social interaction (mating and fighting for food)	Filtration of seawater contaminated with neoplastic cells
Gender specificity	None	None	None
Primary tumours	Genitalia	Face, body	Haemolymph
Metastasis	Rare	70% for DFT1, unknown for DFT2	100% (invade all tissues)
Mortality	Rare	Close to 100% for DFT1 and DFT2	Can be up to 100%
Economic value of host species	100s of billions of US$ per year worldwide for the pet industry	Unquantified but important for Tasmania's tourism industry. Tasmanian devil is listed as endangered by IUCN.	23 billion US$ per year worldwide for the aquaculture industry

database and Google Scholar for relevant publications with specific terms in the topic field, which included the title, abstract, keywords and keywords plus (i.e. words that frequently appear in the titles of the articles cited within a publication). For DFTD, we used the following terms: "Tasmanian devil cancer," "Tasmanian devil facial tumour" and "Tasmanian devil tumour." For CTVT, we used the following terms: "dog transmissive tumour" and "canine transmissible venereal tumour." For DN, we used the following terms: "bivalve neoplasia," "disseminated neoplasia," "bivalve disseminated sarcoma" and "bivalve haemic neoplasia." Until 2016, it was not known whether cases of disseminated neoplasia in marine bivalves were transmissible cancers (Metzger et al., 2016; Yonemitsu et al., 2019); however, due to the phenotypic similarities between the cancerous haemocytes in studies published before and after 2016, we assumed these older cases were also transmissible cancers and pooled them into a single publication group. In addition, for all three groups of transmissible cancers, and to locate additional articles that might not have been identified by the initial search, we checked the reference list of relevant papers based on the predefined keywords. In addition to original research articles, literature reviews were included in our study, because they also facilitate substantive, thorough, sophisticated research to advance our collective understanding of complex topics (Boote & Beile, 2005).

Until August 2019 (i.e. 31 August 2019), we identified 171 publications for DFTD (two lineages), 314 publications for CTVT (one linage) and 112 publications for DN (six lineages), for which we had access to the full text and that met the criteria of our analysis. These publications covered a time period of over 50 years, extending back to 2006, 1963 and 1969 for the three cancers, respectively. The year 1963 corresponded to the year of publication of the oldest study that was found (on CTVT), and for which we were able to access the full text. Thus, we excluded any studies published before this date from the analysis.

For each publication, we determined: (1) the number of citations up to 31 August 2019 using Google Scholar (due to its broader coverage than the Web of Science and Scopus databases, Harzing & Alakangas, 2016), (2) the list of institution(s) involved in the study based on the affiliations of each authors (i.e. universities, zoos, private companies, governmental organizations), each institution being considered only once per publication when represented multiple times, the geographical coordinates of the cities mentioned in the affiliation lists, (3) the total number of unique institutions, (4) whether the publication was an international collaboration which included institutions from more than one country and (5) the great circle distance (in km) between the location of the institution and the site in which the disease was described the first. As reference points, we used Saint Petersburg in which the first experiment demonstrating CTVT was transmissible was conducted (Novinsk, 1876), Tasmania for DFTD (Pearse & Swift, 2006) and Oregon Bay for DN (Farley, 1969). We expected institutions located close to these sites to be the first ones that studied the respective transmissible cancers.

In addition, to determine the scope of the journals in which studies on transmissible cancer are published, the subject area(s) of each journal in which the articles were published was determined using the Scopus subject area classification (which classifies journals into 27 major thematic areas, Elseiver, 2012).

2.2 | Analysis of temporal and geographical trends

The citation data collected for each of the three cancer types represent a cross-sectional study. We, therefore, used linear regression models to investigate how publications accumulated citations over time, Poisson regression models to investigate trends in the number of institutions involved in a publication and logistic regression models to investigate the percentage of publication involving an international collaboration or published in a journal with more than once subject area (Zuur, Ieno, Walker, Saveliev, & Smith, 2009). Full details of model fitting and validation are provided in Supplementary Method 1.

2.3 | Social network analysis

A social network is a collection of social actors, each of which is acquainted with some subset of the others (Newman, 2001, see Supplementary Method 2 for a description of the social network related terms we use in this publication). Using the affiliation for each author involved in transmissible cancer studies, we created a series of one-mode social networks (termed as observed network), in which each institution is a node and each collaboration between two institutions is an undirected link (Opsahl, Vernet, Alnuaimi, & George, 2017, Supplementary Methods 2). The weight of each link was calculated as the number of collaborations between two institutions over a given period of time. Institutions tend to aggregate in collaborative groups that may be isolated from each other (e.g. Mazaris, Gkazinou, Almpanidou, & Balazs, 2018, Supplementary Methods 2).

To quantify the circulation of information within each of these collaborative groups, we computed the average path length, which measures the average shortest distance between two nodes (i.e. by how many institutions the nodes are separated from each other on average). The average path length is an indication of the speed at which information sequentially travels in the network. In addition, we computed the network clustering coefficients, which ranged between 0 (no connection between any of the nodes) and 1 (all the nodes are connected to each other). These were interpreted as the probability that two institutions within a collaborative group are involved into a published study over a given period of time (Barabási et al., 2002; Bunn, Urban, & Keitt, 2000; Minor & Urban, 2008; Opsahl et al., 2017). Furthermore, to investigate whether social networks could be classified as small-world networks, we computed a small-world-ness coefficient by comparing the clustering and path length of a given network to an equivalent random network with same degree on average (following Humphries & Gurney, 2008). A small-world-ness coefficient $\gg 1$ indicates a network with small-world properties.

Then, we used simulations to diagnose the type of networks formed between the institutions collected from the studies on the three transmissible cancers. In a simulation, the number of nodes, the number of links per node, the number of links per publication and the starting point of each link are kept identical to the observed network; however, the end point of each link was allowed to connect to any institution to generate a simulated network, in which any institution randomly collaborates with any other institution (following Opsahl et al., 2017). For the circulation of information between scientists, such simulated random networks are inefficient; thus, comparing the metrics calculated from the observed network to these networks allows the efficiency of the scientific collaboration network to be quantified (Opsahl et al., 2017). Simulations were repeated 1,000 times. For each iteration, the average path length, the clustering coefficient and the small-world-ness coefficient of the simulated network were computed. These three metrics were also computed from the observed networks, and compared with the distributions obtained from the simulations. This approach allows a probabilistic interpretation of the metrics. Values falling outside the distributions generated from the simulations show that the network properties deviate from those of a random network (Opsahl et al., 2017). To identify possible temporal changes to network structure, the whole procedure was repeated using a 3-year moving window for 2006–2019 for DFTD (n = 20–62 institutions), 2005–2019 for CTVT (n = 17–160 institutions) and 2007–2019 for DN (n = 12–37 institutions). The size of the moving window and the length of the time series were chosen to maximize the number of publications (minimum of 12) used to compute the observed networks and simulations. To ensure that the moving time windows did not affect our outputs, we repeated the analyses with a 5-year time window.

2.4 | Reporting of statistical results and software

All statistical analyses were performed in the Bayesian framework. Throughout, we report the estimated parameters followed by their 95% credible intervals in parentheses (Kruschke, 2015). All Bayesian models were computed using the MCMCglmm package (Hadfield, 2010) in R software version 3.3.2. (R Development Core & Team, 2013), and the models were fitted using noninformative priors (Hadfield, 2010). Social network metrics and simulations were performed using the Igraph R package (Csardi & Nepusz, 2006). Geographical data were assimilated using the RWorldmap package (South, 2011).

3 | RESULTS

3.1 | Temporal trends in studies on transmissible cancer

The number of studies on CTVT and DN steadily increased between 1963 and 2006 (Figure 1a), with studies on DFTD first being published in 2006. After 2006, the number of published studies for all

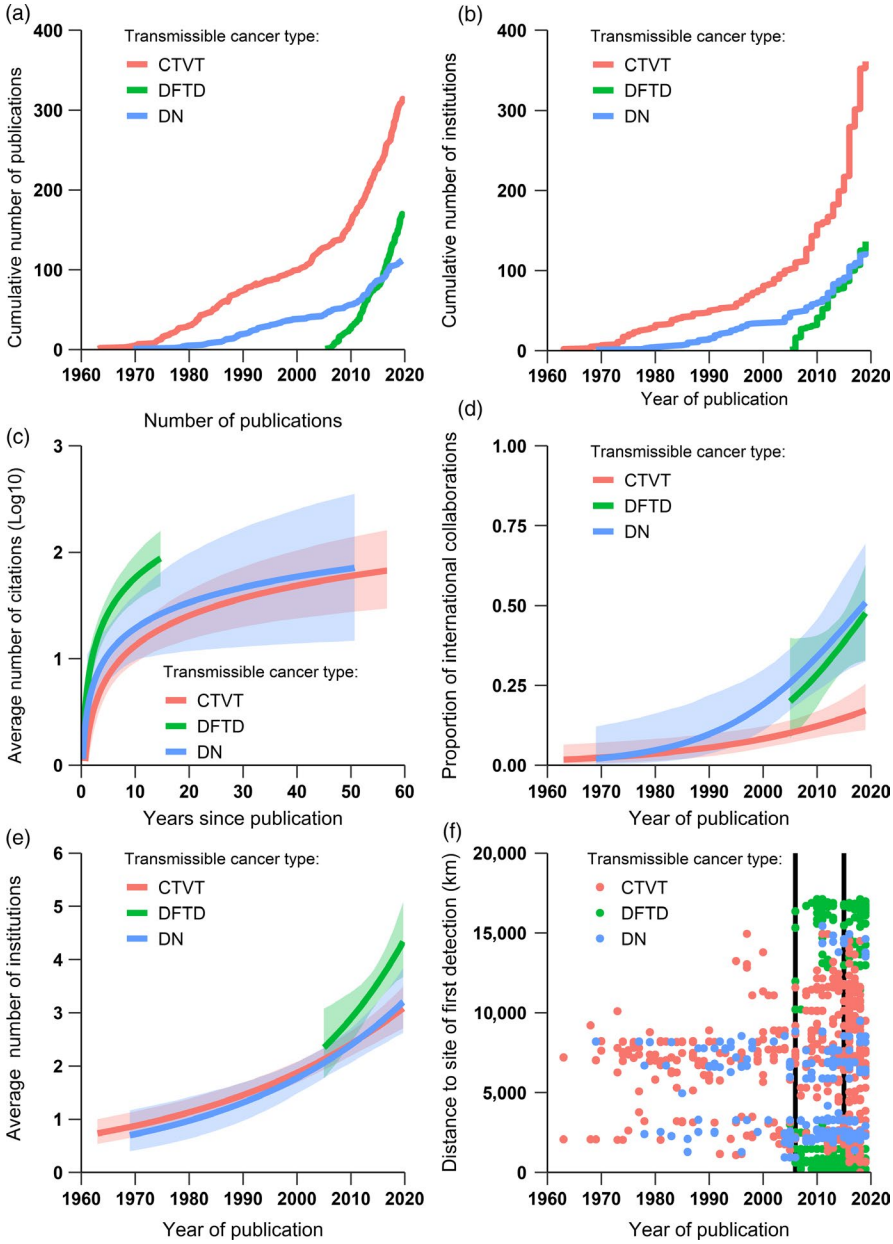

FIGURE 1 General overview of the publications for the three types of transmissible cancer since the first publication for each to 31 August 2019. Cumulative number of (a) publications and (b) institutions involved in the study of transmissible cancers; (c) average number of citations received as a function of the time elapsed since initial publication; (d) proportion of publications involving at least one international collaboration; and (e) average number of institutions involved in a publication. The error bands in (b-e) represent the 95% credible intervals of the estimates. (f) Distance to the first site of detection for institution involved in publications on transmissible cancers. The vertical black line in 2006 shows the start of the boom in Internet technology, but also the year DFTD1 lineage was demonstrated to be a transmissible cancer, while the line in 2015 represents the year DN was demonstrated to be a transmissible cancer

three transmissible cancer types increased about three to four times faster. Studies on DFTD published in 2009 (10 years ago) and 2017 (two years ago) accumulated 3- to 5-fold and 2- to 3-fold more citations, respectively, than studies on CTVT and DN in the same years (Table 2, Figure 1c).

Cumulatively, 136, 359 and 126 institutions were involved in studies on DFTD, CTVT and DN, respectively. The increase in the number of institutions closely matches the number of publications for each cancer type (Figure 1a, b). The number of institutions involved in a publication increased over time and at a similar rate for all three transmissible cancer types (Figure 1e). Over the past 10 years, studies on CTVT were consistently less likely to be an international collaboration compared to DFTD and DN, in which almost half of the studies are international collaboration (Figure 1d).

3.2 | Geographical trends in studies on transmissible cancers

The geographical distribution of the institutions varied among the three transmissible cancer types (Figures 1f, 2) and was correlated with the distribution of the diseases. Two main periods were delineated. In the first period, spanning 1963 to 2006, studies on CTVT or DN were mostly located in Europe or North America, with occasional collaborations between the two continents. In the second period, spanning 2006 to 2019, the number of publications quickly increased, and collaboration networks became global (Figure 1f). For example, during this period, countries in South America started studying CTVT. Interestingly, when DFTD was first described in 2006, scientists almost immediately established international collaborations between Australia, Europe and North America, despite the endemic status of the disease.

TABLE 2 Summary statistics of studies for each of the three transmissible cancer systems

	DFTD	CTVT	DN
	Average number of citations for studies		
Published 2 years ago	10.0 (95% CI 6.8–15.1)	3.8 (95% CI 2.7–3.9)	2.9 (95% CI 1.8–4.8)
Published 10 years ago	57.5 (95% CI 34.6–94.8)	13.2 (95% CI: 9.2–19.2)	19.3 (95% CI: 9.6–39.7)
Published 20 years ago	–	25.4 (95% CI: 15.2–43.9)	33.8 (95% CI: 11.8–98.2)
	Average number of institutions involved in a study		
Published 2 years ago	4.0 (95% CI 3.5–4.5)	2.9 (95% CI 2.6–3.3)	3.0 (95% CI 2.5–3.6)
Published 10 years ago	2.9 (95% CI 2.4–3.4)	2.4 (95% CI 2.2–2.6)	2.4 (95% CI 2.0–2.7)
Published 20 years ago	-	1.9 (95% CI 1.7–2.1)	1.8 (95% CI 2.5–2.1)
	Proportion of studies that are international collaboration		
Published 2 years ago	43% (95% CI 32–55%)	16% (95% CI 11–23%)	47% (95% CI 31–64%)
Published 10 years ago	27% (95% CI 16–40%)	12% (95% CI 8–16%)	41% (95% CI 28–64%)
Published 20 years ago	–	5% (95% CI 5–12%)	32% (95% CI 22–44%)

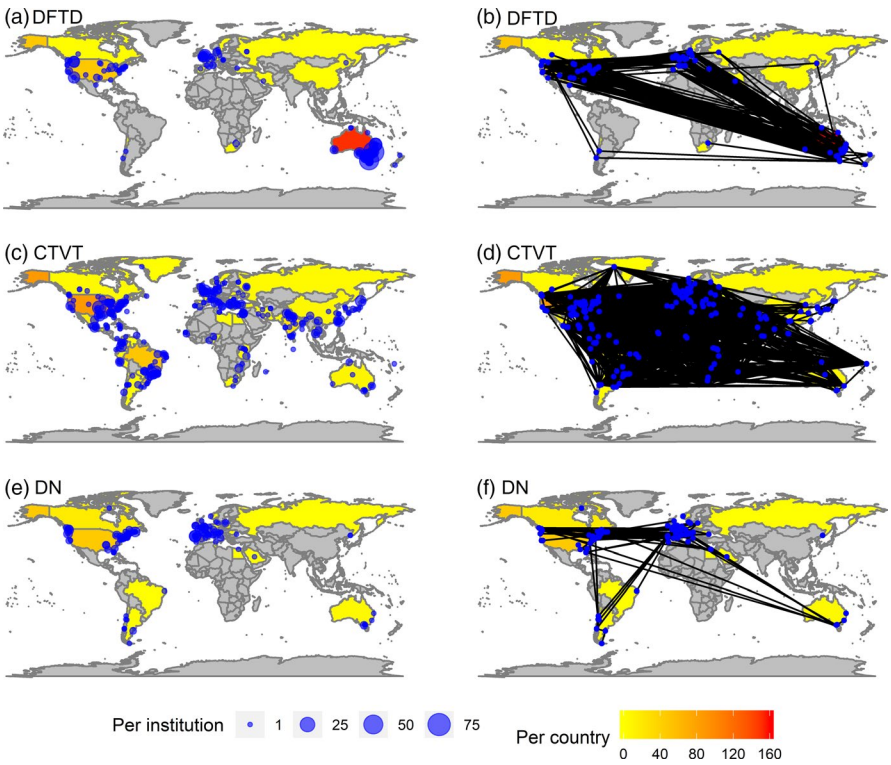

FIGURE 2 Global overview of publications and social networks. Number of publications per country (yellow to red colour scale) and number of publications per institution (blue circles) for (a) DFTD, (c) CTVT and (e) DN. Representation of social network of collaborations between the institutions studying transmissible cancers for (b) DFTD (2005–2019), (d) CTVT (1968–2019) and (f) DN (1969–2019). Each blue circle represents the geographical location of an institution and each solid black line a collaboration between two institutions

3.3 | Multidisciplinary aspect of studies on transmissible cancer

A total of 19 subject areas were identified from the journal scope summaries, in which the studies on the three transmissible cancers were published. Six subject areas encompassed most of the publications (87%) on transmissible cancer (Figure 3). Over the last 50 years, the proportion of studies published in a journal with more than one subject area decreased by half for CTVT (with just 25% of studies being published in such journals by 2019), but slightly increased for DN (to 25% of studies) (Figure 3a). Over the last 10 years, studies published in journals with more than one subject area tripled for DTFD, reaching 75% of studies (Figure 3a). In comparison, the two other transmissible cancers remained relatively constant over the same period. Studies on DFTD are primarily published in journals covering two Scopus major subject area categories ("Agricultural and Biological Sciences" and "Biochemistry, Genetics and Molecular Biology," Figure 3b). In comparison, most (57%) studies on CVTV are published in journals covering Veterinary subject areas (Figure 3c). Studies on DN are primarily published in journals covering the subject areas of Agricultural and Biological Sciences (Figure 3d).

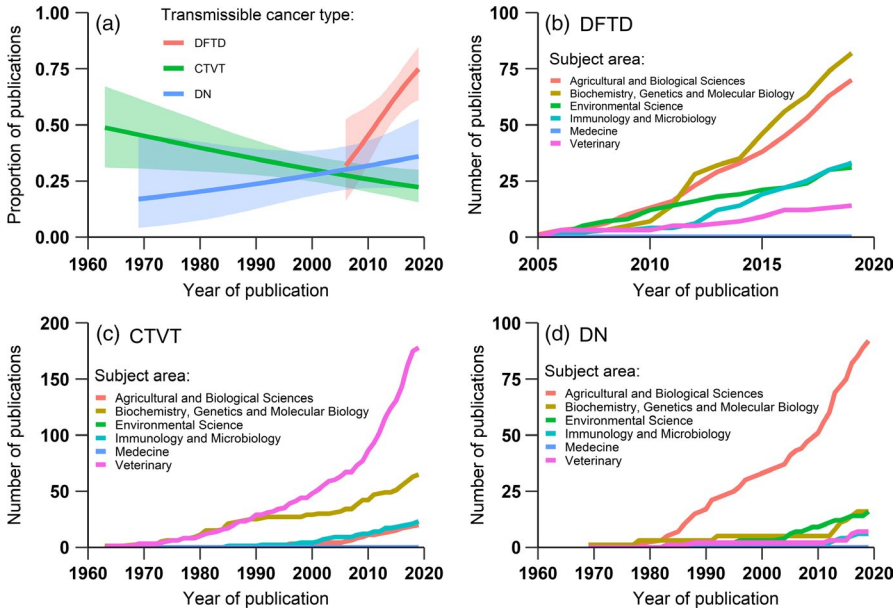

FIGURE 3 (a) Proportion of studies on transmissible cancer published in a journal with more than one subject area. (b) Repartition expressed in cumulative number of publications per year for the six main subject areas in which studies on (b) DFTD, (c) CTVT and (d) DN are published

4 | SOCIAL NETWORK ANALYSIS

The social networks built for institutions studying the three transmissible cancers clearly differed at a global scale, due to variation in the number and geographical distribution of institutions, but also of the diseases (Figure 2b, d, e).

Over a moving three-year or five-year timeframe, the simulations showed that the average path length of the collaborative groups formed by institutions working on DFTD was similar to the simulated random networks indicating a relative lower efficiency compared to a network with a small average path length. For example, the average path length of the collaborative groups was similar to that of institutions working on CTVT and DN but was also smaller compared to the average path length obtained from simulated random networks, indicating relatively efficient networks (Figure 4a-c, Supplementary Results 1).

All of the collaborative groups for the three transmissible cancers had a clustering coefficient greater than those of simulated random networks, with a relatively high average probability that two institutions collaborate over a 3-year or 5-year time period (Figure 4d-f). This indicates a high probability that two institutions working on a transmissible cancer system at a given time are collaborating. However, institutions studying DFTD were about 41% less likely to collaborate with another institution studying DFTD at a given time compared to CTVT and DN.

The networks of collaborations on CTVT and DN exhibited clear small-world properties with relatively high small-world-ness coefficients (often > 10 and up to 90), indicating a relatively dense contact network. However, while also exhibiting small-world properties, the networks of collaboration on DFTD had lower overall small-world-ness coefficients of about 2.5, indicating that these institutions are less efficient at forming connections. In addition, the collaboration networks of intuitions studying CTVT lost most of their small-world-ness, decreasing from a coefficient of about 60 in 2005–2014 to 6 in 2015–2019, indicating a loss of connection between institutions.

The combination of short path lengths and high clustering coefficients, and high small-world-ness coefficients for the three types of transmissible cancers indicates that scientists and their institutions are forming small-world type networks where institutions are on average a short number of collaborations away from every other institution in the network, while at the same time retaining dense local connections. Thus, scientists studying transmissible cancers are organizing themselves into collaborative networks that may maximize efficiency.

5 | DISCUSSION

This study demonstrated a clear evolution in the number of publications, cross-institutional collaborations and international collaborations for CTVT and DN over the past 50 years, along with the acceleration of this trajectory for DTFD since its first observation over 20 years ago. Thus, researchers on DFTD have utilized and applied the benefits of collaborative networks to combat this transmissible disease. Our results reflect those obtained for the evolution of collaborative networks in other systems, including conservation, physics and genetics (ATLAS Collaboration, 2012; Mazaris et al., 2018; The International Cancer Genome Consortium, 2010). In addition, our analyses provide a quantitative foundation on which to formulate effective response systems to new outbreaks of transmissible cancers or other diseases.

The spatiotemporal trends observed in this study show collaborations have expanded over the last 50 years. For instance, collaborations on CTVT and DN were focused in the northern hemisphere before 2006, subsequently becoming global. Researchers on these diseases formed small-world networks in which information is assumed to travel relatively efficiently (Barabási et al., 2002; Newman, 2001; Opsahl et al., 2017). Observed clustering coefficients were larger and average path lengths were smaller compared to certain

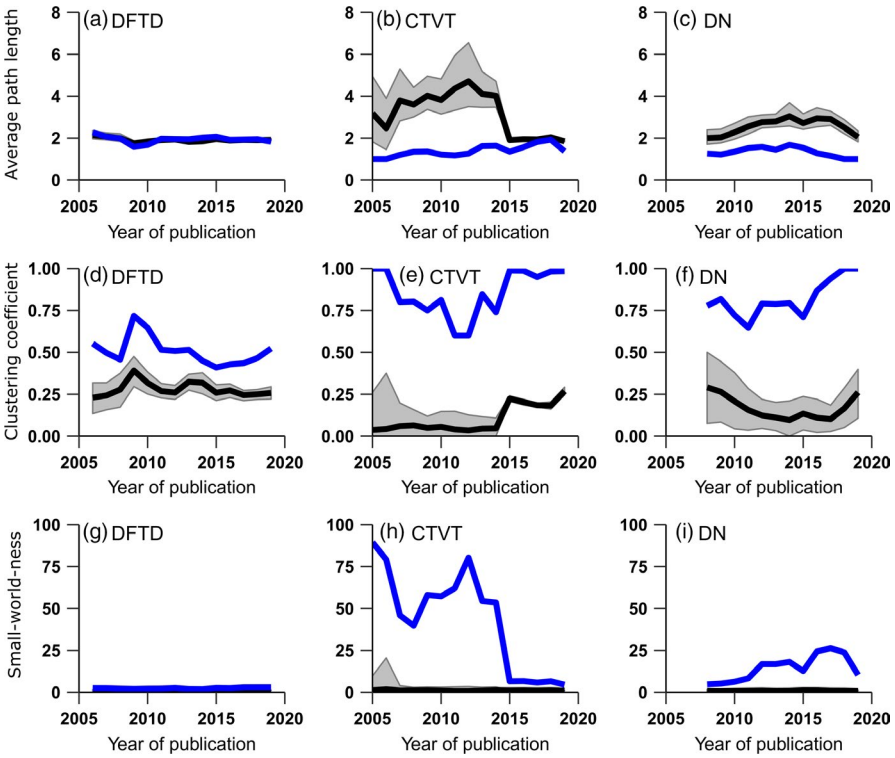

FIGURE 4 Three-year average path lengths of the observed networks (bold blue lines) and the distribution of the average path lengths obtained from the simulation of random networks (average in black bold line and 95% CI in grey) for affiliations studying (a) DFTD, (b) CTVT and (c) DN. Three-year clustering coefficients of the observed networks (bold blue lines) and the distribution of the clustering coefficients obtained from the simulation of random networks (average in bold black lines and 95% CI in grey shading) for affiliations studying (d) DFTD, (e) CTVT and (f) DN. Three-year small-world-ness coefficients of the observed networks (bold blue lines) and the distribution of the small-world-ness coefficients obtained from the simulation of random networks (average in black bold lines and 95% CI in grey) for affiliations studying (g) DFTD, (h) CTVT and (i) DN

fields of science. This included condensed matter studies, mathematics or even the field of biology as a whole (Newman, 2004; Opsahl et al., 2017). Those metrics were however similar to those of the field of psychiatry or the field of physics as a whole (Newman, 2004; Wu & Duan, 2015), indicating a relative efficiency at forming collaborative networks. This increased flow in information was reflected in an increase in the number of publications and institutions involved in studying these cancers and in obtaining new insights. The enhanced scientific collaboration and output since 2006 were likely facilitated by the rapid growth in the Internet and other communication technologies that allow quick and long-distance (face-to-face) communication between scientists located in different countries (Wagner & Leydesdorff, 2005). The year 2006 was also the year DFTD was described and the novelty of this discovery may also partially explain the increase in the number of publications for this cancer type (while it may be too early to see any effect of DN which was only shown to be a transmissible cancer in 2015). In addition, increased mobility through cheaper travel options also likely contributed to this phenomenon (Scellato, Franzoni, & Stephan, 2015). This is especially well illustrated with studies on DFTD, in which Australian scientists immediately established efficient international collaborative networks overseas, producing publications that have accumulated citations much faster than the two other transmissible cancers. However, while substantial insights have been obtained on DFTD (in a very short period of time, see, e.g., Figure 1), the full potential of the scientific community to study DFTD has not yet been reached, as the network shows smaller small-world-ness properties compared to the two other diseases. Low small-world-ness values indicate that the communication and the establishment of collaborations between institutions studying DFTD are not optimal and that there is more potential for collaborations between these institutions (Opsahl et al., 2017). A possible explanation for this is that Tasmanian devils are only found in a relatively small geographical area, making it more difficult to obtain data and to establish collaborations compared to DN and CTVT which are globally distributed. This unexploited potential might not be compatible with the rapid decline of Tasmanian devil populations (Lachish, McCallum, & Jones, 2009; Lazenby et al., 2018) and with the relatively high risk of emergence of new types of tumours (two independent transmissible cancers appeared between 1996 and 2019, Pye et al., 2016; Stammnitz et al., 2018). This species will likely require collaborations as efficient as possible to mitigate the effect of transmissible cancers (Hamede et al., 2019).

There are multiple benefits in forming collaborative networks to obtain insights on transmissible cancers. Efficient and highly connected networks are required to develop effective ways to mitigate their negative effect. This phenomenon is illustrated in the field of medicine, in which large-scale multidisciplinary collaborations have developed operational strategies to combat infectious diseases, such as the human immunodeficiency virus and antibiotic-resistant bacteria (Årdal et al., 2016; Deeks et al., 2016). Currently, studies on DFTD and DN primarily focus on obtaining insights on the diseases and how they affect ecosystems (Carballal, Barber, Iglesias, & Villalba, 2015; Cunningham et al., 2018; Cunningham, Scoleri, Johnson, Barmuta, & Jones, 2019; Hollings, Jones, Mooney, & Mccallum, 2014; Lazenby et al., 2018; Metzger et al., 2016; Stammnitz et al., 2018). So far, cures have not been found (e.g. Ikonomopoulou & Fernandez-Rojo, 2018), with only an efficient, and now, routine treatment existing for CTVT (with vincristine, Birhan & Chanie, 2015). While research for

a vaccine to prevent DFTD is currently in progress (Kreiss, Brown, Tovar, Lyons, & Woods, 2015), the collective effort of scientists from multiple fields is required, with no guarantee of success. Similarly, institutions studying DN are concentrated in Europe and North America, and have traditionally focused on topics of marine biology, with expertise on bivalve biology and farming (Guo, Xu, Feng, & Zhang, 2016; Wijsman, Troost, Fang, & Roncarati, 2018); thus, extending this network to incorporate other disciplines and to those already working on transmissible cancers could prove beneficial. Both Europe (5.5% of the global production 2010–2015 period) and North America (9.9% of the global production when pooled with South America) export shellfish, but in much lower quantities compared to Asia, which represents almost all of the remaining global production (Wijsman et al., 2018). Paradoxically, the country with the largest production of bivalves in the world, China, has no institution studying DN and publishing results in English-language journals, despite the recent rapid increase in scientific output from this country (Mazloumian, Helbing, Lozano, Light, & Börner, 2013). Furthermore, cases of DN have been reported in Asia since 2000 (in Japan, Usheva & Frolova, 2000; and the Philippines, Vera et al., 2005), suggesting it is likely present in China.

Current key challenges in obtaining insights on transmissible cancers include determining how many actually exist (Ujvari et al., 2016b), as well as their evolutionary ecological impact, especially in the context of increased pressure on ecosystems and the economy (Hamede et al., 2019; Preece et al., 2017). Transmissible cancers can only emerge under the confluence of specific conditions, termed the "perfect storm" (Ujvari et al., 2016b). For contagious cancer cells lines to emerge, several micro- and macro-environmental factors (e.g. permissive immune system, presence of transmission routes, optimal conditions to survive in transport), and tumour cell traits (high proliferation rate, genetic and phenotypic plasticity, shedding of high number of cells etc.) must align. Transmissible cancers present a selective force on the host akin to parasites and may have been critical drivers of major transitions during the evolution of multicellular organisms, such as the origin of sexual reproduction (Thomas et al., 2019) and the development of the immune systems (Ujvari, Gatenby, & Thomas, 2017). Thus, transmissible cancers represent an essential, but so far understudied, selective force during the evolution of organisms, and ultimately in ecosystem functioning. Therefore, to understand these fascinating novel and complex host–parasite systems extensive research collaborations encompassing multidisciplinary teams (with expertise in oncology, immunology, physiology, ecology, mathematical modelling and immunology) are required. Consequently, the study of transmissible cancers offers a great opportunity to create multidisciplinary and efficient collaborations.

Our findings demonstrate that a team that discovers a new type of transmissible cancer, or more broadly a new infectious disease, should immediately form collaborations with key institutions already working on these diseases, as well as with expertise from other key fields including ecology, oncology, immunology, anatomy, biochemistry and physiology. Such action would facilitate rapid access to the required knowledge, allowing the development of strategies to limit the spread of the disease, as well as to moderate potential emerging threats to the affected ecosystem and economy. In particular, we demonstrated that this strategy facilitates the fast generation of knowledge (represented by publications) based on the trajectory of collaborative research on DFTD. Publications and associated citations are considered as a relatively reliable measurement of impact and quality within the scientific community, as long the trajectories are compared over similar timeframe (Aksnes & Rip, 2009).

6 | CONCLUSIONS

This study demonstrated that, despite exhibiting differences in their global geographical distribution, institutions working on transmissible cancers organize themselves into highly connected small-world networks. It is likely that scientists establish collaborations with specialists in the target area, as well as supporting fields or research, to develop effective action strategies.

AUTHORS CONTRIBUTION

AMD, GS and BU designed the study, AMD and GB collected the data, AMD performed the statistical and social network analyses, and AMD, GS and BU led the writing of the manuscript with inputs from NR, TF and RHR.

DATA AVAILABILITY STATEMENT

The sources of the data used in this publication are described in the methods section (Web of Science, Scopus and Scimago websites).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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