

'Where the Wind Comes Sweeping Down the Plain': Using a Bibliometric Study to Identify Trends and Knowledge Gaps of Vector-borne Disease Research in Oklahoma

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Abstract. Research on vector-borne diseases on the Great Plains has a rich and dynamic publication history. The aim of this study was to assess the publication trends in Oklahoma between 1965 and 2015 with a view to identifying knowledge gaps on which to focus future research initiatives. Using Web of Science (Thompson Reuters) and Pubmed (National Center for Biotechnology Information) in EndNote, a total of 747 publications was identified that involved Oklahoma-based researchers, samples, or data obtained since 1965. Eighty-two percent (n = 615) of the published studies focused on ticks and tick-borne diseases. Most of the studies involving specific tick species (n = 282) focused on the lone star tick, *Amblyomma americanum* (L.), (51.1%), with anaplasmosis the primary disease system studied. Until 1989, most vector-borne disease research focused on ecology and control. The trend shifted almost complementarily since the 1990s with as much as 80% of research focused on clinical- or laboratory-based studies. This study found a rich diversity of research on vector-borne diseases in Oklahoma during the past 5 decades, most of which need greater attention. At least 30 universities in Oklahoma that provide 2-year associate degrees to underserved populations provide excellent possibilities from which to address important questions regarding vector-borne diseases.

Introduction

Research on vector-borne diseases on the Great Plains has a rich and dynamic history. The history is most often remembered through stories or antidotes from old colleagues, but the best record comes through the publications during a period of time. The published record provides insights into the priorities of given time periods and is often used as a means to measure success. In the last 2 decades, these kinds of studies have focused on trends in biomedical research involving the topic in general (Ducrot et al. 2016, Martinez-Pulgarin et al. 2016), specific journals (Peccora et al. 2016), countries or regions (Dandona et al. 2009 (India), Sweileh et al. 2015 (Arab countries), Aaron et al. 2010 (West Africa), Boyce et al. 2015 (Somaliland), Noden 2013 (Namibia)), and specific disciplines (Lewison and Srivastava 2008 (malaria), Ramos et al. 2013 (leishmania)). Only a few have focused on vector-borne disease research in particular countries (Russell 1998 (Australia), Cuisance and Rioux 2004 (France), Ram 2015 (India)). To date, no

study has assessed trends and gaps in knowledge for vector-borne disease research within a given state in the United States.

Research on vector-borne diseases has been published in Oklahoma since before the 1930s, with an increased pattern of change in funding and personnel during the last 5 decades. The aim of this study, therefore, was to assess publication trends in Oklahoma between 1965 and 2015 with a view to identifying trends and knowledge gaps that need specific attention.

Materials and Methods

Web of Science® (Thompson Reuters, New York, NY) and Pubmed® (National Center for Biotechnology Information, Bethesda, MD) in EndNote® (Thompson Reuters, New York) were used to create a file of publications focused on medical and veterinary entomology based on keywords, key researchers, and Oklahoma. Criteria included were any peer-reviewed manuscript associated with an arthropod involved in medical and veterinary entomology (covered in Mullen and Durden 2009) between 1965 and June 2015. Keywords used included common and scientific names for vectors (examples: tick, lone star, *Amblyomma*, mosquito, *Culex*, *Aedes*, *Anopheles*, flea, sandfly, kissing bug, *Triatoma*, *Culicoides*, horse fly, tabanids, wasp, swallow bug, bee, and ant) or diseases (examples: arbovirus, West Nile, western equine, *Ehrlichia*, *Rickettsia*, Rocky Mountain spotted fever, *Anaplasma*, malaria, *Babesia*, *Leishmania*, *Trypanosoma*, *Dirofilaria*, heartworm, tularemia, *Francisella*, *Borrelia*, Lyme disease) AND Oklahoma. Also, all researchers who worked in any area related to medical and veterinary entomology in Oklahoma between 1965 and 2015 were searched. Care was given to ensure the employment history of each researcher so only the work published during the period in which the researchers were working in Oklahoma-based institutions was included. This process involved personal research, discussions with the authors, and verification of address trails listed in many of the publications.

Once created in Endnote, the file was converted into Excel® (Microsoft, Inc., Redmond, WA) and further modified to be able to be descriptively analyzed using SPSS (version 21, IBM Corp., Armonk, NY). During the process, every publication citation was vetted to ensure the reference was a peer-reviewed manuscript and that at least one author was affiliated with an Oklahoma-based entity or a sample or data reported in the published work was from Oklahoma. While every effort was made to account for all published papers during the 40-year period, because of the variety of places where articles can be published, it was not possible to claim the search was exhaustive.

The publications were sorted into those primarily focused on clinical/lab-based research and ecology/control-based research. Because much of the early work in Oklahoma focused on basic ecology and control of vectors, the two broad categories were used to differentiate between laboratory- and field-based research. The clinical/lab-based studies involved all aspects of medical focus including host/cell lines/pathogen biology/ diagnostics/treatments/pathogenesis, and lab-based research included studies completed within a laboratory setting with no obvious link to field sampling. Field-based research focused on control and prevention, mostly in field settings, as well as epidemiology and vector competence studies.

Results

In total, 781 publications were identified that focused on some aspect of vector-borne disease in Oklahoma, of which 747 involved Oklahoma-based researchers or samples/data. Of the publications on vector-borne diseases in Oklahoma since 1965, 82% (615/747) focused on ticks and tick-borne diseases. Other areas included: bugs (bedbugs, *Triatoma*, and swallow bugs (n = 34, 4.6%), mosquitoes (n = 30, 4.0%), flies (bot/cattle grubs, face and house flies, Culicoides, sandflies, tsetse flies, and tabanids) (n = 26, 3.5%), *Hymenoptera* (n = 17, 2.3%) and other systems such as caterpillars (n = 1), fire ants (n = 4), fleas (n = 6), lice (n = 1), mites (n = 2), and general ectoparasites (n = 8). Although all publications fit loosely under the term 'medical and veterinary entomology', 47% (355 of 747) did not directly involve the vector but focused only on the pathogen(s) or parasite(s) transmitted by a particular vector. Of the 615 publications that focused on ticks and tick-borne diseases, only 29% focused on the ecology and control of ticks, with most (71%) focused on laboratory-based or clinical studies not directly involving the arthropod. This contrasted with publications involving other vector-borne diseases of which 60% focused on ecology and control.

Most studies involving specific tick species (n = 282) focused on lone star ticks, *Amblyomma americanum* (L.) (51.1%) while the rest involved the Rocky Mountain wood tick, *Dermacentor andersoni* Stiles (12.4%) (a species not native to Oklahoma but a principal vector for anaplasmosis in the northwestern United States), American dog tick, *Dermacentor variabilis* Say (7.1%); blacklegged tick, *Ixodes scapularis* Say (6.0%); Gulf coast tick, *Amblyomma maculatum* Koch (5.6%); brown dog tick, *Rhipicephalus sanguineus* (Latreille) (4.2%); and winter tick, *Dermacentor albipictus* (Packard) (1.4%). Other tick species (one or two studies each) were the cattle tick, *Rhipicephalus (Boophilus) microplus* (Canestrini); rabbit tick, *Haemaphysalis leporispalustris* (Packard); *Ixodes baergi* Cooley and Kohls; *Ixodes woodi* Bishopp; spinose ear tick, *Otobius megnini* (Dugès); and *Ornithodoros concanensis* Cooley and Kohls.

The disease systems on which Oklahoma-based research was focused were expansive. Anaplasmosis (30%) was the most studied system, followed by ehrlichiosis (14%), canine hepatozoonosis (7%), babesiosis (5%), Rocky Mountain spotted fever (5%), Buggy Creek virus (5%), Lyme disease (4%), cytauxzoonosis (4%), tularemia (4%), and venom (4%). An additional 17% of the studies focused on mosquito arboviruses, Bluetongue, *Bartonella*, *Moraxella*, plague, Q fever, murine typhus, trypanosomiasis/Chagas disease, leishmania, malaria, myiasis, dirofilariasis (canine heartworm), and scabies.

The scope of vector-borne research has changed extensively since 1965 (Fig. 1). Between 1965 and 1989, most research on vector-borne disease focused on ecology and control aspects of medical and veterinary entomology. This trend shifted almost complementarily since the 1990s with as much as 80% of research involving clinical- and laboratory-based studies and 20% focused on ecology and control.

The two main entities involved in vector-borne disease research in Oklahoma since 1965 were the School of Veterinary Medicine and Department of Entomology at Oklahoma State University (Fig. 2). Interesting patterns of publication varied through the decades between the two institutions that also involved a growing number of other Oklahoma-based institutions. Before 1970, only three institutions

were involved in vector-biology research. The number increased to 15 between 2000 and 2009 and was already at 13 since 2010.

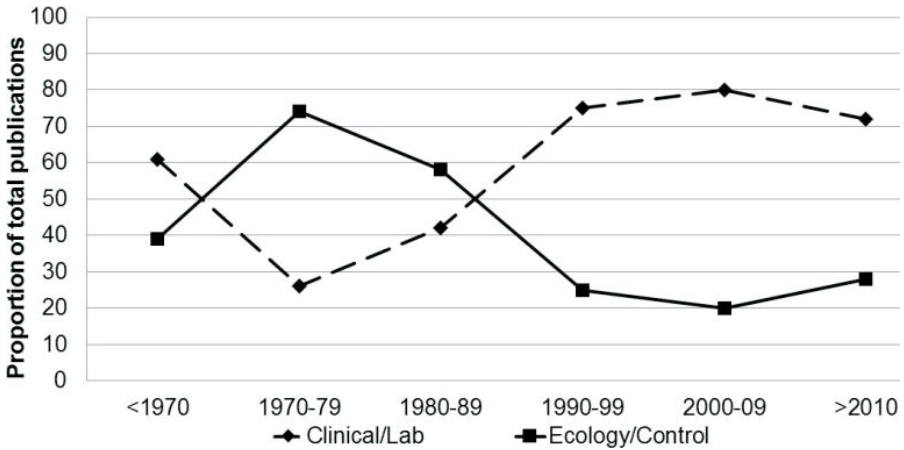


Fig. 1. Proportion of published studies completed between 1965 and 2015 by focus of study.

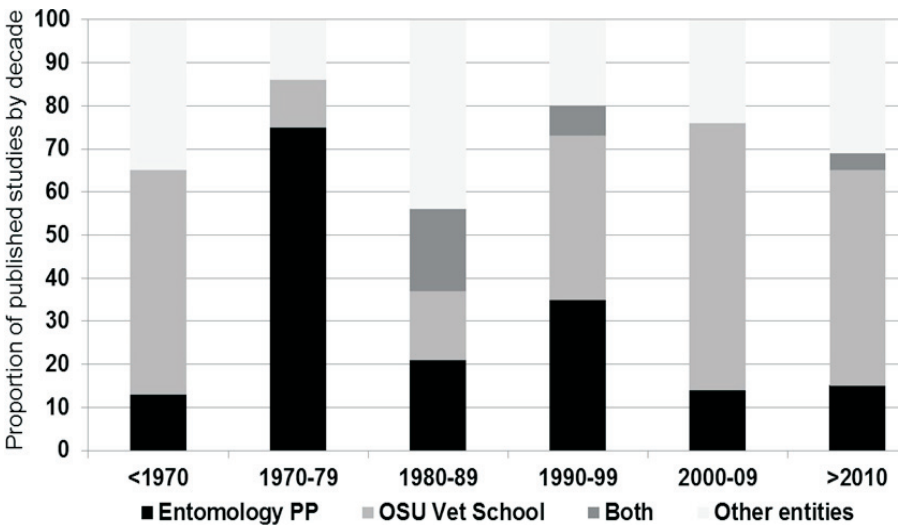


Fig. 2. Proportion of published studies completed by various Oklahoma-based entities by decade between 1965 and 2015. "Other entities" include institutions inside and outside of Oklahoma.

Discussion

A rich diversity of research on vector-borne diseases has occurred in Oklahoma since 1965. While the focus has been on ticks and/or tick-transmitted diseases, a remarkable variety of research has focused on research based in Oklahoma or samples/data obtained from Oklahoma. It was obvious that most of the research published was not necessarily based on the needs of the state but was because of funding priorities or expertise/priorities of individual researchers present during a given period of time. This is even more obvious in the area of ticks and tick-borne diseases.

During the 1970s and 1980s, most tick research in Oklahoma was by the Department of Entomology at OSU and a federally-funded ARS program at Poteau at the Lone Star tick research facility focused on understanding the ecology of *A. americanum*. In addition to basic ecological studies, the focus was on the effects of Lone star tick on cattle and methods for eliminating the tick species from vast areas of the country. When funding ended for the projects at the end of the 1980s, the priority and some of the researchers moved from the arthropod to the biology and pathogenesis of the pathogens transmitted by the ticks. That trend has continued until the present to the extent that most published studies since the 1990s have focused on clinical- and laboratory-based projects (Fig. 1). Because of significant changes in funding priorities and personnel, important aspects related to ecology and control of ticks and tick-borne diseases need updating and clarification.

The shift of focus from field- to laboratory-based research in the 1980s led to failure to detect significant geographical change in distribution of *A. americanum* during the past 40 years. Mainly limited to eastern Oklahoma in the 1960s and 1970s (Semtner et al. 1971), active surveillance in 2014 demonstrated this important tick vector was established in all of eastern and central Oklahoma as well as many western counties (Barrett et al. 2015). Passive surveillance through submissions of tick samples to the K. C. Emerson Entomology Museum in the Department of Entomology and Plant Pathology at Oklahoma State University confirms the spread of this important tick between the 1970s and 2000s (Grantham unpublished data). This unmonitored expansion is most likely responsible for the dramatic increase in incidence of spotted fever group rickettsiosis and ehrlichiosis that occurred in Oklahoma since 2000 (Noden and Bradley unpublished data).

Together with unmonitored changes in tick vector distribution, it has been left to nationally-focused publications to identify occupational, social, and cultural practices contributing to increased risk for tick-borne diseases among humans in Oklahoma. Keep in mind that all the studies used data reported from Oklahoma – but are written by persons mainly focused on tick-borne disease from a national perspective. Some examples include:

- 1) During the last 3 decades, the incidence of Rocky Mountain spotted fever (Holman et al. 2009, Folkema et al. 2012a) and ehrlichiosis (Folkema et al. 2012b) dramatically increased among Native American communities in Oklahoma. For reasons not yet identified, members of Native American communities are two to four times more likely to be infected with one or both of the tick-borne diseases compared with the population at large.
- 2) Oklahoma is third in the United States for incidence of tularemia, with limited epidemiological focus on the problem (CDC 2013). Data indicate that 50% of the cases were caused by tick bites (K. Bradley, State epidemiologist, personal

communication), but no data exist concerning social, occupational, or cultural risk factors that might lead to infection.

- 3) The nature of *Borrelia* sp. infections in Oklahoma ticks has not been characterized for more than 3 decades. While the risk of Lyme disease in Oklahoma was discussed in the early 1990s (Reiner et al. 1991, Lawrence et al. 1992), it is not considered a problem because immature *I. scapularis* in Oklahoma prefer to feed on lizards instead of mice (Garvin et al. 2015). Recently, however, reports have claimed increased exposure to Lyme-infected ticks by local community members (Donley 2015, Noden personal communication). Several Oklahoma-based studies have reported results from canine Lyme surveillance in the context of the United States (Bowman et al. 2009, Little et al. 2014), but no tick-focused surveillance has evaluated the prevalence of *B. burgdorferi* in Oklahoma-collected ticks since 1990 (Kocan et al. 1992). The national distribution map of *I. scapularis* was recently updated (Dennis et al. 1998, Eisen et al. 2016) but there is need for local ground truthing and establishing the phenology and activity patterns of this important tick species within the state. The main activity peak for adult *I. scapularis* is considered to be in October/November, with a smaller activity peak in February/March, yet we still do not know the best time of day or night to collect adult ticks. Additionally, no study has presented the distribution of STARi (Southern Tick-Associated Rash Illness associated with *A. americanum*), *Anaplasma phagocytophilum*, or other *Borrelia* sp. such as *B. miyamotoi* (CDC 2015) or *B. mayonii* (CDC 2015) associated with *I. scapularis* in northern states.
- 4) Both emerging tick-borne virus infections, Heartland virus (CBS News 2014) and Bourbon virus (KFOR News 2015), have occurred in Oklahoma since 2014. Both patients were males occupationally exposed to ticks. There is an additional need to identify the unique occupations on the Great Plains that are most at risk for tick-borne diseases so that targeted education programs can be developed to alert and reduce risks of persons engaged in those occupations.
- 5) Because of the exceptional focus on ticks and tick-borne diseases by Oklahoma-based research teams since 1965, basic information on 'other' vector-borne diseases is needed. This includes identification and distribution of important species, ecology of vectors in a variety of environments, and specific control and preventative measures that consider specific regional ecological constraints. Examples include:
 - 1) **Flea-borne rickettsiosis.** Recent studies demonstrated that opossums and their fleas have been involved in point epidemics of flea-borne typhus caused by *R. typhi* or *R. felis* at Austin, TX (Adjemian et al. 2010), with new cases occurring at Galveston, TX (Blanton et al. 2015). Only two Oklahoma-based studies suggested the presence of *R. typhi* in Oklahoma. Wilcomb (1952) reported 28 human cases caused by *R. typhi* in Oklahoma between 1939 and 1948, and Marshall et al. (2000) identified antibodies to *R. typhi* in sick children from hospitals at Oklahoma City. Both used serological methods prone to misidentification because of cross-reactivity of antibodies. The only flea study in the state was by a USDA researcher who drove through Oklahoma on a single business trip and picked up flea samples from prairie dogs (*Cynomys* spp.) in Canadian and Ellis counties in May 2004 (Reeves et al. 2007). In the 17 fleas collected, undetermined rickettsial DNA was detected in one *Oropsylla hirsuta* (Baker) flea from the Ellis County site. Additionally, an unreported number of fleas from a commercial colony that

originated from wild-caught fleas at Stillwater, OK were tested using early molecular methods (Higgins et al. 1994). Of those tested, 83% of *R. felis* (ELB-agent) were positive. To date, virtually nothing is known regarding important flea-borne diseases in Oklahoma nor have flea vectors or potential hosts been identified.

- 2) **Leishmaniasis.** The first report of autochthonous Leishmania in Oklahoma was from an outbreak of 16 dogs at a private kennel in the north-central region of Oklahoma in 1979 (Anderson et al. 1980). Later, in 2003 and 2005, human cases were identified when a physician reported two cases of autochthonous cutaneous leishmaniasis in McCurtain County, southeastern Oklahoma (Clarke et al. 2013). The parasite that probably caused the human cases was considered to be *Leishmania mexicana* and this unique event was drought-related. No other components of the ecology (the rodent reservoir hosts (woodrats) or sand fly vectors) have been identified in Oklahoma.
- 3) **Trypanosomiasis.** The first reports of *Trypanosoma cruzi* in Oklahoma were serologically confirmed (3.6%) in a group of naturally exposed canines (Bradley et al. 2000). In this report, *Trypanosoma cruzi* was reported as 'enzootic' in eastern Oklahoma with the probable vector identified as *Triatoma sanguisuga*. To date, no published study focused on the ecology and potential risks of the disease in Oklahoma, despite the increased regional attention on this topic (Garcia et al. 2015, Wozniak et al. 2015).
- 4) **Relapsing Fever.** Cases of autochthonous relapsing fever were reviewed and reported between 1934 and 1942 in five western Oklahoma counties (Alfalfa, Grant, Harper, Kiowa, and Washita) (Fisher 1942). Infected *Ornithodoros turicata* (Dugès) were collected in Kiowa and Washita counties. All human cases were diagnosed by observing spirochetes in the blood or via symptoms. One case study recounted how a family was infected when they took refuge in their storm shelter, were 'stung' by numerous infected *Ornithodoros turicata* arthropods, and all developed symptoms 5 days later. No cases have been published since that time.
- 5) **Other Possible Pathogens in Oklahoma.** To date, plague (*Yersinia pestis* – flea-transmitted) is considered a rare disease in Oklahoma with the last reported case in 1991, associated with exposure to prairie dogs in the Oklahoma Panhandle (OKDH 2016). Cat-scratch fever (*Bartonella henselae* – flea-transmitted) has not been published in the state. Reeves et al. (2007) collected 14 fleas from prairie dogs at two locations and found uncharacterized Bartonella DNA in six samples. Uncharacterized *Bartonella* sp. also were identified in blood from Oklahoma cattle (Chang et al. 2000).
- 6) **Biting Flies.** In general, only limited or dated information is available on any biting fly species that mainly impact livestock, especially ecological aspects of development and adult-resting sites based on unique ecological components.

While there are information gaps regarding vector-borne disease systems needing attention in Oklahoma, most research during the past 5 decades has been by one institution. This is relatively normal in states with few 4-year research-focused institutions. It does seem, however, that 'other' research entities in the state, especially 2-year universities that award associate degrees, have become more involved in the last 15 years. More than 30 universities in Oklahoma provide 2-year associate or higher degrees to students from underserved populations

including Hispanic, Native American, African-American, rural, and first-generation college attendees. If networked effectively, the institutions could provide unique and creative opportunities for undergraduates from the communities to engage in research that directly impacts health in the state while being mentored by faculty engaged in research or by collaboration with individuals from larger research-focused institutions.

In summary, focus has been on research on vector-borne diseases in Oklahoma during the last 5 decades. There are, however, major gaps in knowledge of important aspects of many disease systems which keeps us from realizing the true impact of the systems on public and veterinary health in the state. The encouraging trend of developing small, but effective research network relationships into small institutions in regions where a specific disease is more likely to occur might stimulate more involvement in research by unserved populations in the state.

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