A review of rat lungworm infection and recent data on its definitive hosts in Hawaii

Chris N. Niebuhr,[1] USDA, APHIS, Wildlife Services, National Wildlife Research Center, Hawaii Field Station, P.O. Box 10880, Hilo, HI 96721, USA *niebuhrc@landcareresearch.co.nz*

Susan I. Jarvi, Department of Pharmaceutical Science, Daniel K. Inouye College of Pharmacy, University of Hawaii at Hilo, 200 W. Kawili Street, Hilo, HI 96720, USA

Shane R. Siers, USDA APHIS Wildlife Services, National Wildlife Research Center, Hawaii Field Station, P.O. Box 10880, Hilo, HI 96721, USA

Abstract: Rat lungworm (*Angiostrongylus cantonensis*) is a zoonotic nematode that causes rat lungworm disease (angiostrongyliasis), a potentially debilitating form of meningitis, in humans worldwide. The definitive hosts for rat lungworm are primarily members of the genus *Rattus,* with gastropods as intermediate hosts. This parasite has emerged as an important public health concern in the United States, especially in Hawaii, where the number of human cases has increased in the last decade. Here we discuss the current knowledge of the rat lungworm, including information on the life cycle and host species, as well as updates on known infection levels. Three species of rats have been unintentionally introduced and become established in Hawaii (*Rattus exulans*, *R. norvegicus*, and *R. rattus*), all of which have been documented as definitive hosts of rat lungworm. Our recent findings indicate that infection levels in rats can vary by species and age. Based on these findings, we also suggest the possibility that *R. rattus* populations in Hawaii are capable of developing some form of acquired immunity to infection over time, which could have important management implications related to control operations. Information on rat lungworm infection levels and distribution in Hawaii is lacking, especially in rat definitive hosts, and the U.S. Department of Agriculture (USDA) National Wildlife Research Center and the University of Hawaii at Hilo are continuing efforts to help fill these gaps in knowledge.

Key words: acquired immunity, *Angiostrongylus cantonensis*, disease, Hawaii, prevalence, rat, *Rattus*

Angiostrongylus cantonensis (Nematoda: Metastrongylidae), or the rat lungworm, is a parasitic nematode that causes rat lungworm disease (angiostrongyliasis) in humans and other animals worldwide. The definitive hosts of rat lungworm are rats (Rodentia: Muridae), with snails (Mollusca: Gastropoda) acting as intermediate hosts. Paratenic (transport) hosts can also be involved in transmission. While infected intermediate or paratenic hosts are the source of human (and other animal) infection, rat definitive hosts are required for sexual reproduction of the parasite.

Angiostrongylus cantonensis was first discovered from a 1931–1932 survey of parasites in rats from Canton (now Guangzhou) China (Chen 1933) and was formally described a few years later (originally as *Pulmonema cantonensis*; Chen 1935). This survey reported *A. cantonensis*

from *Rattus rattus* (black, ship, or roof rat) and *R. norvegicus* (brown or Norway rat), with 10.7% (9/84) of rats infected (1/38 *R. rattus*; 6/17 *R. norvegicus*, and 2/29 *Rattus* spp. unidentified). The first reported case of human infection by *A. cantonensis* was in Taiwan in 1944 (Nomura and Lin 1945, translated to English in Beaver and Rosen 1964). Since then, infections in humans, domestic animals, and wildlife have been recorded elsewhere in Southeast Asia and India, Africa, the Pacific Islands, the Americas, and the Caribbean, with more recent reports from Australia, the continental United States, and the Canary Islands (Wang et al. 2008, Martin-Alonso et al. 2011, York et al. 2014, Spratt 2015, Barratt et al. 2016). Observations of *A. cantonensis* beyond its historical subtropical locations, in more temperate locations, has raised some concerns regarding its current

---

[1]Present address: Manaaki Whenua – Landcare Research, P.O. Box 69040, Lincoln 7640, New Zealand

global distribution and increasing potential for spread, due to introductions, host expansion, and climate change (York et al. 2014, 2015; Stockdale Walden et al. 2017).

The first report of *A. cantonensis* in the Americas was from Cuba in 1981 (Aguiar et al. 1981), and the first report from the continental United States was from Louisiana in 1988 (Campbell and Little 1988). Both discoveries were from wild *R. norvegicus* hosts, with 60% (12/20) and 21.4% (20/94) of rats observed positive for *A. cantonensis*, respectively. The first reported human infection with *A. cantonensis* in North America was from Louisiana in 1993 (New et al. 1995). However, in Hawaii, the parasite was discovered a few decades earlier, with the first documentation from a 1960 survey of parasites in wild rats (*R. rattus* and *R. norvegicus*) on Oahu that reported 12% (9/75) of rats infected with *A. cantonensis* (Ash 1962). Based on 2 patients in Hawaii that became sick in 1959 and died in 1960, it was theorized and later confirmed that *A. cantonensis* was a causative agent of eosinophilic meningitis (Horio and Alicata 1961, Alicata 1962, Rosen et al. 1962, Alicata 1991). This was the first time, globally, a direct link was made between this nematode species and human disease. Since then, the number of human cases of angiostrongyliasis in Hawaii have increased significantly, including reports from each of the 6 most populated islands (Hawaii Island, Kauai, Lanai, Molokai, Maui, and Oahu; Kliks and Palumbo 1992, Cowie 2017, Jarvi et al. 2018). Here we discuss current knowledge of *A. cantonensis* host species and infection levels, with emphasis on rat definitive hosts in Hawaii.

Human angiostrongyliasis

Human infections with *A. cantonensis* typically occur from intentional or unintentional ingestion of infected intermediate or paratenic hosts, sometimes due to contaminated produce. Humans are considered accidental or dead-end hosts, meaning the parasite is unable to complete its normal life cycle (as seen in rats) and ultimately dies within the host's body. Rat lungworm disease is seen in the central nervous system after ingested larval stages of *A. cantonensis* migrate to the brain and spinal cord, molt to sub-adult stages, and supposedly die after being unable to re-

enter the circulatory system (Wang et al. 2012, Cowie 2013, Prociv and Turner 2018). The combination of the movement of the worms in the brain tissue and the person's immune system response to the dying worms likely both contribute to the neurological damage that can occur (Graeff-Teixeira et al. 2009, Cowie 2017). Clinical symptoms vary from mild to severe and can include headaches, nausea, encephalitis, paralysis, and sometimes death (Wang et al. 2012, Howe 2013, Cowie 2017). The variability of symptoms along with limitations in diagnostic testing have likely resulted in the underreporting of infections in humans (Al Hammoud et al. 2017, Howe and Jarvi 2017).

Life cycle

The life cycle of *A. cantonensis* is complex, requiring both rat definitive hosts and gastropod intermediate hosts for the development of sexual and asexual parasite stages, respectively (Figure 1). The life cycle can sometimes involve a range of paratenic hosts (e.g., prawns, crabs, frogs), which act as substitute hosts until another host is reached; however, they do not support larval development. During the complete life cycle, 5 larval stages of *A. cantonensis* exist (L_1–L_5) along with a sexually mature adult stage. The L_1 larvae, present in rat feces, are consumed by snails and molt twice into L_3 larvae in approximately 2 weeks, with the development rate influenced by temperature (Mackerras and Sandars 1955). While L_3 larvae can also occur in paratenic hosts, the molting process would have occurred previously in the snail prey. The L_3 larvae are infective to potential definitive or accidental hosts that may consume infected intermediate or paratenic hosts. Some evidence exists suggesting that it is also possible to become infected directly by L_3 larvae found outside an intermediate or paratenic host; however, more investigation is needed to confirm how likely or frequently this occurs (Cheng and Alicata 1964*a*, Heyneman and Lim 1967, Richards and Merritt 1967, Qvarnstrom et al. 2013). Within the host, L_3 larvae migrate passively through the bloodstream where some ultimately reach the brain and molt twice into young adults (L_5) in approximately 4 weeks. In the case of humans and other accidental hosts, the life cycle is often thought to end with the larvae dying in the central nervous system,
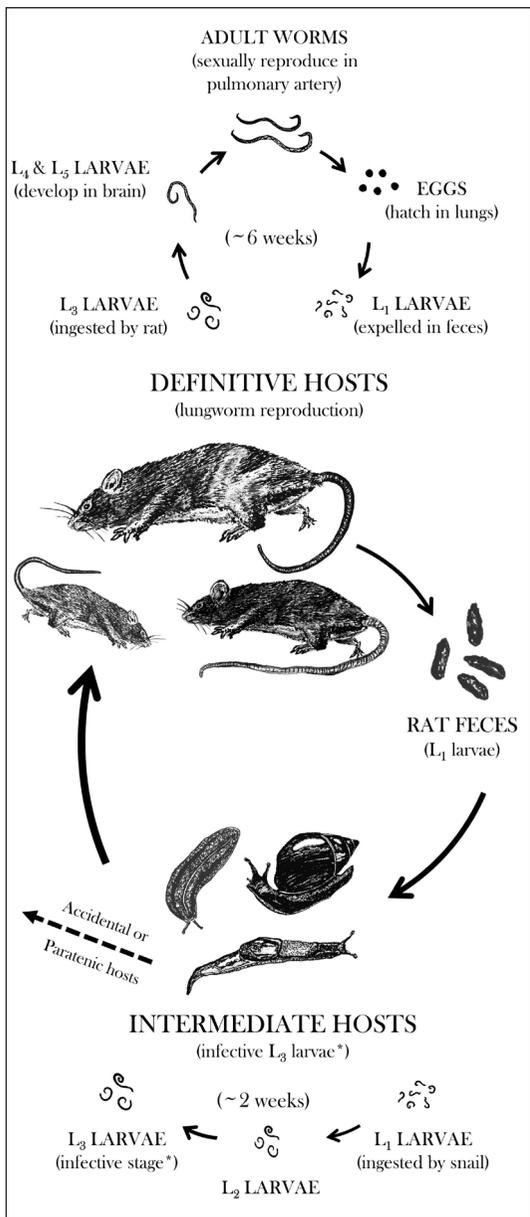
Figure 1. The life cycle of the rat lungworm (*Angiostrongylus cantonensis*) in both definitive hosts (e.g., rats) and intermediate hosts (e.g., snails and slugs). *Indicates the parasite stage that is infective to humans (artwork by I. Leinbach).

although observations have been made of adult worms in the lungs of children autopsied in Australia (Prociv and Turner 2018). In the rat definitive hosts, however, the L_5 larvae migrate to the pulmonary artery where they fully develop into male and female adults. After fertilization and oviposition, eggs migrate to the lungs and hatch into L_1 larvae in the lung tissue of the rat (giving the rat lungworm

its name). The L_1 larvae then migrate up the trachea, are swallowed, and released in the feces (Mackerras and Sandars 1955, Bhaibulaya 1975, Chao et al. 1987). This exit from the rat host to the environment occurs approximately 2 weeks after the L_5 larval stage initially reached the pulmonary artery. Thus, under the assumption that an infective L_3 larvae is consumed by a rat immediately upon completing the molting stage in the snail, the entire life cycle of *A. cantonensis* takes approximately 8 weeks. Although rats are the obligate definitive host, some evidence has been shown that infection can lead to death (Mackerras and Sandars 1955).

Hosts
Intermediate hosts

A wide variety of intermediate hosts have been identified for *A. cantonensis* globally, including species from as many as 51 gastropod families (Barratt et al. 2016). In Hawaii, both native and non-native snail species (including slugs) can act as hosts, with varying infection levels observed among species (Hollingsworth et al. 2007, Kim et al. 2014). One Hawaii survey identified the presence of *A. cantonensis* in 2 native and 14 non-native snail species, including common farm and garden species such as the giant African snail (*Lissachatina fulica*) and the Cuban slug (*Veronicella cubensis*; Kim et al. 2014). Of particular concern is the invasive semi-slug (*Parmarion martensi*), which has been documented to carry heavier parasite burdens and higher rates of infection than other gastropod hosts in Hawaii (Hollingsworth et al. 2007, Kim et al. 2014).

Paratenic hosts

Paratenic hosts act as reservoirs for infective *A. cantonensis* larvae, which, when consumed by humans or other animals, can lead to infection. Crustaceans (e.g., freshwater prawns, land crabs; Cheng and Alicata 1964*b*, Rosen et al. 1967), land planarians (or flatworms) (Alicata 1962, Ash 1976), centipedes (Wang et al. 2018), reptiles (Radomyos et al. 1994), and amphibians (e.g., frogs, toads; Ash 1968, Lai et al. 2007) have all been identified as paratenic hosts, some of which have been directly linked to human infection. Fish (Wallace and Rosen 1967) and mammals (e.g., pigs, cows; Cheng and Alicata 1964*c*, Jindrak and Alicata 1968)

have also been explored as possible paratenic hosts; however, their transmission potential to humans has not been determined.

Examples of human infections from paratenic hosts include people consuming raw frogs and centipedes infected with *A. cantonensis*, which directly led to cases of eosinophilic meningitis (Lai et al. 2007, Wang et al. 2018). A recent study by our research group has reported *A. cantonensis* infections in frogs, toads, and centipedes in Hawaii (Niebuhr et al. 2020), and while these species are not known to be consumed by humans, reports exist of consumption by rats (Abernethy et al. 2016). Land planarians, which are predators and scavengers of gastropods, have also been implicated as sources of human infection. In New Caledonia, Ash (1976) reported that the majority of cases of eosinophilic meningitis, which occurred during and just after the cool season, were directly associated with the influx of infected planarians in gardens supplying produce to local markets, and not with known snail intermediate hosts found in the area, due to their seasonal population trends. Similarly, in Japan, planarians have also been suggested as important sources of human infection, with 1 species of concern being active throughout the year (Asato et al. 2004). In Hawaii, planarians have been identified as infected with *A. cantonensis*, although their significance as a source of infection to humans or rats is unknown (Qvarnstrom et al. 2010, 2013).

Accidental vertebrate hosts

Angiostrongylus cantonensis infection has been reported in numerous non-human vertebrate species, including domestic animals and wildlife. In many cases, individual animals have displayed symptoms, sometimes severe, and in other cases infection has led to death. Angiostrongyliasis has been observed in dogs and horses (Costa et al. 2000, Lunn et al. 2012, Spratt 2015), as well as captive wildlife including non-human primates, marsupials, bats, and birds (Aguilar et al. 1999, Reddacliff et al. 1999, Monks et al. 2005, Burns et al. 2014). Infections with *A. cantonensis* have also been observed in species in the wild, with varying degrees of symptoms displayed (Barrett et al. 2002, Ma et al. 2013, Dalton et al. 2017). Impacts of *A. cantonensis* on wildlife species could potentially have detrimental consequences for the conservation of animals in and around zoos, wildlife rehabilitation centers, or populations in the wild (Spratt 2015). Some wildlife species have also been identified as possible biosentinels and may be useful in monitoring the spread of *A. cantonensis* in certain areas (Ma et al. 2013, Spratt 2015). Little is known regarding angiostrongyliasis in non-human vertebrates in Hawaii, although this may be attributed to difficulties in diagnostics and overall lack of investigation. However, in recent years, probable cases in dogs and horses have been reported on Hawaii Island by local veterinarians (S. Jarvi, University of Hawaii at Hilo, personal communication).

Definitive hosts

Various murid rodent species have been identified as definitive hosts of *A. cantonensis* worldwide, primarily rats of the genus *Rattus* and other closely related genera (Yong and Eamsobhana 2013). *Mus musculus* (house mouse), a smaller murid rodent species, is reported to be an accidental dead-end host, with some observations of infection leading to death (Mackerras and Sandars 1955, Alicata and McCarthy 1964, Kinsella 1987). In Hawaii, where the only native terrestrial mammals are bats, 3 introduced rat species are present: *R. exulans* (Polynesian or Pacific rat), *R. rattus*, and *R. norvegicus*. The smallest rat species, *R. exulans*, is thought to have arrived with early Polynesian colonizers, possibly as early as 1219–1266 A.D. (Wilmshurst et al. 2011). In Hawaii, *R. exulans* is not considered commensal, and prefers forested or agriculture habitats (Tomich 1969, Tobin 1994). *Rattus rattus* may have arrived during 1870–1890 (Atkinson 1977), and populations span a wide variety of habitats including commensal, forested, and agriculture (Tomich 1969, Shiels et al. 2014). *Rattus norvegicus* is the largest rat species in Hawaii. It is thought to have arrived from 1825–1842 (Kramer 1971) and is associated mostly with commensal habitats such as urban/ suburban and agriculture, especially sugarcane (Tomich 1969, Timm and Squill 1994). A brief review of diets of each rat species can be found in Shiels and Pitt (2014). In Hawaii, all 3 *Rattus* species have been identified as definitive hosts of *A. cantonensis*, with varying degrees of observed prevalence (Table 1). Due to the lack of data on

Table 1. Observed prevalence levels of adult *Angiostrongylus cantonensis* infection levels in the lungs and pulmonary arteries of rat definitive host species (*Rattus* spp.) in Hawaii, USA.

Year(s) sampled	*Rattus* host species	Observed prevalence		Island	Reference
		Morphological identification (adult stage)	Molecular identification (all stages)		
1960[a]	*R. rattus, R. norvegicus*[b]	9/75 (12%)[c]	-	Oahu	Ash (1962)
1961–1964	*Rattus* spp.[b]	186/475 (39.2%)	-	Hawaii	Wallace and Rosen (1965)
1961–1964	*R. exulans*	17/17 (100%)	-	Kauai	Wallace and Rosen (1965)
1961–1964	*R. rattus*	2/3 (66.7%)	-	Kauai	Wallace and Rosen (1965)
1961–1964	*R. norvegicus*	11/16 (68.8%)	-	Kauai	Wallace and Rosen (1965)
1961–1964	*R. exulans*	0/64 (0%)	-	Molokai	Wallace and Rosen (1965)
1961–1964	*R. rattus*	0/320 (0%)	-	Molokai	Wallace and Rosen (1965)
1961–1964	*R. exulans*	6/14 (42.9%)	-	Oahu	Wallace and Rosen (1965)
1961–1964	*R. rattus*	33/97 (34%)	-	Oahu	Wallace and Rosen (1965)
1961–1964	*R. norvegicus*	8/9 (88.9%)	-	Oahu	Wallace and Rosen (1965)
(~50-year gap in published research)					
2009, 2011	*R. exulans*	5/10 (50%)	10/10 (100%)	Hawaii	Qvarnstrom et al. (2013)
2009, 2011	*R. rattus*	14/26 (53.8%)	26/26 (100%)	Hawaii	Qvarnstrom et al. (2013)
2009, 2011	*R. norvegicus*	1/1 (100%)	1/1 (100%)	Hawaii	Qvarnstrom et al. (2013)
2012–2013	*R. rattus*	10/61 (16.4%)	-	Hawaii	Jarvi et al. (2015)
2017	*R. exulans*	186/200 (93%)	198/200 (99%)	Hawaii	Jarvi et al. (2017)
2017	*R. rattus*	178/310 (57.4%)	280/310 (90.3%)	Hawaii	Jarvi et al. (2017)

[a]The sampling year for Ash (1962) is reported in Alicata (1991).
[b]Prevalence was not reported for individual species.
[c]The parasite stage observed was not reported.

spatial and temporal variables influencing *A. cantonensis* infections in Hawaii, as well as any variation in host trapping methodologies used, these infection rates can be difficult to interpret, and caution should be used when attempting to compare them.

Differences in infection levels also varied within the same study and for the same individuals sampled, based on the method of parasite detection used. Both morphological and molecular identification methods have been used for detecting *A. cantonensis* infection in rat definitive hosts, including in Hawaii. Morphological identification of eggs and larval stages from host tissue, blood, or fecal samples is possible through various histopathological methods (e.g., tissue squashes, suspension in liquid) that require high magnification (Stokes et al. 2007, Jarvi et al. 2017). For adult worm identification, the host's heart, lungs, and pulmonary arteries are removed and examined under a dissecting microscope, with the option to count male and female worms separately. Both the presence/absence and number of adult worms can be used when comparing infection levels between individuals, populations, and species of definitive hosts (Qvarnstrom et al. 2013, Simões et al. 2014, Jarvi et al. 2017). For these morphological identification methods, except the fecal analysis, access to the host animal is required, and samples need to be collected post-mortem. Fecal samples could be collected from the environment (or even rat traps) and used for confirmation of parasite presence; however, this method would not be good for quantifying infection levels due to the difficulty of distinguishing samples among host individuals. The survival of L_1 larvae in host feces is also dependent on various environmental conditions such as moisture and temperature (Sawabe and Makiya 1995). In Australia, where the closely related *Angiostrongylus mackerrasae*

is found, visual identification of L_1 larvae from host feces alone is not helpful, since the L_1 larvae of both nematode species are morphologically indistinguishable (Bhaibulaya 1975).

Molecular identification methods (e.g., real-time PCR), commonly used to detect *A. cantonensis* from intermediate or paratenic hosts (Qvarnstrom et al. 2010, Jarvi et al. 2012, Niebuhr et al. 2020), can also be used for rat definitive hosts (Jarvi et al. 2017). These methods can provide accurate parasite detection down to the species level using a very small amount of sample; however, they typically require the collection of organ tissue post-mortem and are designed to detect any presence of parasite DNA in the host (i.e., any life stage). Detections have been made from blood sampled from the tails of anesthetized rats, but since these detections are a result of larvae circulating within the bloodstream of the host, observations can vary due to the timing of sampling (Jarvi et al. 2015). Molecular identification of L_1 larvae from feces can also be made from either samples collected from the colons of necropsied rats or from the environment (Stockdale Walden et al. 2017). Molecular techniques can also be used to distinguish between genetic lineages of *A. cantonensis*, information which may be of importance when maintaining laboratory strains or conducting experimental studies (Červená et al. 2019). It is important to consider the method of parasite detection when investigating infection levels in both individuals and wild populations of rats.

Differences in infection levels (both prevalence and infection intensity) between rat species have also been observed worldwide (Barratt et al. 2016). *Rattus norvegicus* infection levels have often been reported to be higher than in other rat species (Alicata and McCarthy 1964, Campbell and Little 1988, Deng et al. 2012, Wang et al. 2012), and *R. rattus* levels often reported lower than other rat species, including *R. exulans* (Alicata and McCarthy 1964, Jarvi et al. 2017). Possible explanations for these differences could be related to habitat use or dietary preference (Zhang et al. 2008, Jarvi et al. 2017). Our own study on Hawaii Island (Jarvi et al. 2017), however, reported a higher observed prevalence of adult worm infection in *R. exulans* than *R. rattus*, but the opposite for L_3 larvae infection, data which does not support

the above explanations, but could be explained by differences in host susceptibility or parasite survival. We observed that both prevalence and intensity of infection of adult *A. cantonensis* in *R. rattus* were lower in older than younger individuals within the same population, with younger individuals showing similarly high infection levels observed in *R. exulans*. Older *R. rattus* also showed more evidence of past infections (presence of encysted adult worms) and less evidence of current infections (live adult worms) than younger rats. These observations suggest that wild *R. rattus* in Hawaii develop some form of acquired immunity to *A. cantonensis* over time after exposure. Acquired immunity to *A. cantonensis* has previously been demonstrated in experimental studies using laboratory strains of *R. norvegicus*, showing lower worm burdens after just a single infection, and again in each subsequent infection (Au and Ko 1979, Yong and Dobson 1982, Wang et al. 1989). These findings may have important management implications when considering efforts to control rat populations in areas where *A. cantonensis* is present, particularly for *R. rattus* in Hawaii. For example, it has been shown that if a control operation does not reduce a rat population to very low levels, remaining rats will reproduce rapidly and sometimes even exceed their former density for a short period of time (Marsh 1994). These population eruptions would produce a higher ratio of naïve rats (i.e., younger individuals in this case) that are more susceptible to *A. cantonensis*, which could lead to more infected rats with higher worm burdens in the population than before. Since population numbers and behavior of snail intermediate hosts of *A. cantonensis* are seasonally influenced by rainfall and temperature (Ash 1976, Choi et al. 2004), timing of rat control operations to prevent natural peaks in snail numbers from coinciding with any spikes in rat infection levels might be advisable. Additionally, if any spillover risk exists to rat populations in Hawaii by paratenic hosts acting as disease reservoirs, then these species must also be considered when making management decisions.

Conclusions

The global presence of angiostrongyliasis is increasing (Barratt et al. 2016), and this emerging infectious disease is currently a

public health concern in Hawaii, where recent increases in human cases have been reported (Cowie 2017, Jarvi et al. 2018). To help predict the risk to humans, a better understanding of the epidemiology of this disease is needed, such as factors influencing patterns of infection. Currently, data on infection levels and distribution of *A. cantonensis* in wild host populations throughout Hawaii are severely lacking, especially in regards to the rat definitive host. Although a small number of studies have reported on *A. cantonensis* infections in rats, some at extremely high levels, little is understood regarding the distribution of infection at a landscape scale, particularly in relation to different land uses and climates. Furthermore, preliminary data from ongoing research suggest seasonal fluctuations in infection levels of rat populations in Hawaii (Niebuhr et al., unpublished data), so research priorities going forward should also include temporal investigations. It is also not known what role acquired immunity plays in influencing infection levels in wild rat populations and what implications this may have on future control operations. The USDA National Wildlife Research Center and the Daniel K. Inouye College of Pharmacy at the University of Hawaii at Hilo are continuing to investigate the rat definitive host of *A. cantonensis* in Hawaii, incorporating both experimental infection and field studies.

Acknowledgments

Literature cited

Abernethy E. F., K. L. Turner, J. C. Beasley, T. L. DeVault, W. C. Pitt, and O. E. Rhodes. 2016. Carcasses of invasive species are predominantly utilized by invasive scavengers in an island ecosystem. Ecosphere 7(10): e01496.

Aguiar, P. H., P. Morera, and J. Pascual. 1981. First record of *Angiostrongylus cantonensis* in Cuba. American Journal of Tropical Medicine and Hygiene 30:963–965.

Aguilar, R. F., K. Topham, J. J. Heatley, D. Nichols, J. Cross, R. Bauer, and M. Garner. 1999. Neu-

ral angiostrongylosis in nonhuman primates: diagnosis, treatment and control of an outbreak in southern Louisiana. Proceedings of the American Association of Zoo Veterinarians 1999:272–276.

Al Hammoud, R., S. L. Nayes, J. R. Murphy, G. P. Heresi, I. J. Butler, and N. Pérez. 2017. *Angiostrongylus cantonensis* meningitis and myelitis, Texas, USA. Emerging Infectious Diseases 23:1037–1038.

Alicata, J. E. 1962. *Angiostrongylus cantonensis* (Nematoda: Metastrongylidae) as a causative agent of eosinophilic meningoencephalitis of man in Hawaii and Tahiti. Canadian Journal of Zoology 40:5–8.

Alicata, J. E. 1991. The discovery of *Angiostrongylus cantonensis* as a cause of human eosinophilic meningitis. Parasitology Today 7:151–153.

Alicata, J. E., and D. D. McCarthy. 1964. On the incidence and distribution of the rat lungworm *Angiostrongylus cantonensis* in the Cook Islands, with observations made in New Zealand and Western Samoa. Canadian Journal of Zoology 42:605–611.

Asato, R., K. Taira, M. Nakamura, J. Kudaka, K. Itokazu, and M. Kawanaka. 2004. Changing epidemiology of *Angiostrongyliasis cantonensis* in Okinawa Prefecture, Japan. Japanese Journal of Infectious Diseases 57:184–186.

Ash, L. R. 1962. The helminth parasites of rats in Hawaii and the description of *Capillaria traverae* sp. n. Journal of Parasitology 48:66–68.

Ash, L. R. 1968. The occurrence of *Angiostrongylus cantonensis* in frogs of New Caledonia with observations on paratenic hosts of Metastrongyles. Journal of Parasitology 54:432–436.

Ash, L. R. 1976. Observations on the role of mollusks and planarians in the transmission of *Angiostrongylus contonensis* infection to man in New Caldonia. Revista de Biologia Tropical 24:163–174.

Atkinson, I. 1977. Reassessment of factors, particualarily *Rattus rattus* that influenced the decline of endemic forest birds in Hawaiian Islands. Pacific Science 31:109–133.

Au, A. C. S., and R. C. Ko. 1979. Changes in worm burden, haematological and serological response in rats after single and multiple *Angiostrongylus cantonensis* infections. Parasitology Research 58:233–242.

Barratt, J., D. Chan, I. Sandaradura, R. Malik, D. Spielman, R. Lee, D. Marriott, J. Harkness, J. Ellis, and D. Stark. 2016. *Angiostrongylus can-*

tonensis: a review of its distribution, molecular biology and clinical significance as a human pathogen. Parasitology 143:1087–1118.

Barrett, J. L., M. S. Carlisle, and P. Prociv. 2002. Neuro-angiostrongylosis in wild black and grey-headed flying foxes (*Pteropus* spp.). Australian Veterinary Journal 80:554–558.

Beaver, P. C., and L. Rosen. 1964. Memorandum on the first report of *Angiostrongylus* in man, by Nomura and Lin, 1945. American Journal of Tropical Medicine and Hygiene 13:589–590.

Bhaibulaya, M. 1975. Comparative studies on the life history of *Angiostrongylus mackerrasae* Bhaibulaya, 1968 and *Angiostrongylus cantonensis* (Chen, 1935). International Journal for Parasitology 5:7–20.

Burns, R. E., E. J. Bicknese, Y. Qvarnstrom, M. DeLeon-Carnes, C. P. Drew, C. H. Gardiner, and B. A. Rideout. 2014. Cerebral *Angiostrongylus cantonensis* infection in a captive African pygmy falcon (*Polihierax semitorquatus*) in southern California. Journal of Veterinary Diagnostic Investigation 26:695–698.

Campbell, B. G., and M. D. Little. 1988. The finding of *Angiostrongylus cantonensis* in rats in New Orleans. American Journal of Tropical Medicine and Hygiene 38:568–573.

Červená B., D. Modrý, B. Fecková, K. Hrazdilová, P. Foronda, A. M. Alonso, R. Lee, J. Walker, C. N. Niebuhr, R. Malik, and J. Šlapeta. 2019. Low diversity of *Angiostrongylus cantonensis* complete mitochondrial DNA sequences from Australia, Hawaii, French Polynesia and the Canary Islands revealed using whole genome next-generation sequencing. Parasites & Vectors 12:241.

Chao, D., C. C. Lin, and Y. A. Chen. 1987. Studies on growth and distribution of *Angiostrongylus cantonensis* larvae in Ampullarium canaliculatus. Southeast Asian Journal of Tropical Medicine and Public Health 18:248–252.

Chen, H. T. 1933. A preliminary report on a survey of animal parasites of Canton, China, rats. Lingnan Science Journal 12:65–74.

Chen, H. T. 1935. Un nouveau nématode pulmonaire, *Pulmonema cantonensis* n.g., n.sp., des rats de Canton. Annales de Parasitologie Humaine et Comparée 13:312–317.

Cheng, T. C., and J. E. Alicata. 1964*a*. Possible role of water in the transmission of *Angiostrongylus cantonensis* (Nematoda: Metastrongylidae). Journal of Parasitic Diseases 50:39–40.

Cheng, T. C., and J. E. Alicata. 1964*b*. Land crabs as probable paratenic hosts for the infective larvae of *Angiostrongylus cantonensis*. Journal of Parasitology 50:39.

Cheng, T. C., and J. E. Alicata. 1964*c*. Pigs and calves as carrier hosts for the infective larvae of *Angiostrongylus cantonensis*. Journal of Parasitology 50:39.

Choi, Y. H., D. A. Bohan, S. J. Powers, C. W. Wiltshire, D. M. Glen, and M. A. Semenov. 2004. Modelling *Deroceras reticulatum* (Gastropoda) population dynamics based on daily temperature and rainfall. Agriculture, Ecosystems and Environment 103:519–525.

Costa, L. R. R., J. J. McClure, T. G. Snider, III, and T. B. Stewart. 2000. Verminous meningoencephalomyelitis by *Angiostrongylus* (=*Parastrongylus*) *cantonensis* in an American miniature horse. Equine Veterinary Education 12:2–6.

Cowie, R. H. 2013. Biology, systematics, life cycle, and distribution of *Angiostrongylus cantonensis*, the cause of rat lungworm disease. Hawaii Journal of Medicine & Public Health 72:6–9.

Cowie, R. H. 2017. *Angiostrongylus cantonensis*: agent of a sometimes fatal globally emerging infectious disease (rat lungworm disease). ACS Chemical Neuroscience 8:2102–2104.

Dalton, M. F., H. Fenton, C. A. Cleveland, E. J. Elsmo, and M. J. Yabsley. 2017. Eosinophilic meningoencephalitis associated with rat lungworm (*Angiostrongylus cantonensis*) migration in two nine-banded armadillos (*Dasypus novemcinctus*) and an opossum (*Didelphis virginiana*) in the southeastern United States. International Journal for Parasitology: Parasites and Wildlife 6:131–134.

Deng, Z. H., Q. M. Zhang, S. Y. Huang, and J. L. Jones. 2012. First provincial survey of *Angiostrongylus cantonensis* in Guangdong Province, China. Tropical Medicine and International Health 17:119–122.

Graeff-Teixeira, C., A. C. A. da Silva, and K. Yoshimura. 2009. Update on eosinophilic meningoencephalitis and its clinical relevance. Clinical Microbiology Reviews 22:322–348.

Heyneman, D., and B. L. Lim. 1967. *Angiostrongylus cantonensis*: proof of direct transmission with its epidemiological implications. Science 158:1057–1058.

Hollingsworth, R. G., R. Kaneta, F. F. Sullivan, H. S. Bishop, Y. Qvarnstrom, A. J. daSilva, and D. G. Robinson. 2007. Distribution of *Parmarion* cf. *martensi* (Pulmonata: Helicarionidae), a

new semi-slug pest on Hawaii Island, and its potential as a vector for human angiostrongyliasis. Pacific Science 61:457–467.

Horio, S., and J. E. Alicata. 1961. Parasitic meningoencephalitis in Hawaii. A new parasitic disease of man. Hawaii Medical Journal 21:139–140.

Howe, K. 2013. A severe case of rat lungworm disease in Hawaii. Hawaii Journal of Medicine & Public Health 72:46–48.

Howe, K., and S. I. Jarvi. 2017. Angiostrongyliasis (rat lungworm disease): viewpoints from Hawaii Island. ACS Chemical Neuroscience 8:1820–1822.

Jarvi, S. I., M. E. M. Farias, K. Howe, S. Jacquier, R. Hollingsworth, and W. Pitt. 2012. Quantitative PCR estimates *Angiostrongylus cantonensis* (rat lungworm) infection levels in semi-slugs (*Parmarion martensi*). Molecular and Biochemical Parasitology 185:174–176.

Jarvi, S. I., K. Howe, and P. Macomber. 2018. Angiostrongyliasis or rat lungworm disease: a perspective from Hawaii. Current Tropical Medicine Reports 5:59-66.

Jarvi, S. I., W. C. Pitt, M. E. Farias, L. Shiels, M. G. Severino, K. M. Howe, S. H. Jacquier, A. B. Shiels, K. K. Amano, B. C. Luiz, D. E. Maher, M. L. Allison, Z. C. Holtquist, and N. T. Scheibelhut. 2015. Detection of *Angiostrongylus cantonensis* in the blood and peripheral tissues of wild hawaiian rats (*Rattus rattus*) by a quantitative PCR (qPCR) assay. PLOS ONE 10(4): e0123064.

Jarvi, S. I., S. Quarta, S. Jacquier, K. Howe, D. Bicakci, C. Dasalla, N. Lovesy, K. Snook, R. Mchugh, and C. N. Niebuhr. 2017. High prevalence of *Angiostrongylus cantonensis* (rat lungworm) on eastern Hawaii Island: a closer look at life cycle traits and patterns of infection in wild rats (*Rattus* spp.). PLOS ONE 12(12): e0189458.

Jindrak, K., and J. E. Alicata. 1968. Comparative pathology in experimental infection of pigs and calves with larvae of *Angiostrongylus cantonensis*. Journal of Comparative Pathology 78:371–382.

Kim, J. R., K. A. Hayes, N. W. Yeung, and R. H. Cowie. 2014. Diverse gastropod hosts of *Angiostrongylus cantonensis*, the rat lungworm, globally and with a focus on the Hawaiian Islands. PLOS ONE 9(5): e94969.

Kinsella, J. M. 1987. Studies on the life cycle and host specificity of *Parastrongylus schmidti* (Nematoda: Angiostrongylidae). Proceedings of the Helminthological Society of Washington 54:245–248.

Kliks, M. M., and N. E. Palumbo. 1992. Eosinophilic meningitis beyond the Pacific Basin: the global dispersal of a peridomestic zoonosis caused by *Angiostrongylus cantonensis*, the nematode lungworm of rats. Social Science and Medicine 34:199–212.

Kramer, R. 1971. Hawaiian land mammals. Tuttle Publishing, Clarendon, Vermont, USA.

Lai, C. H., C. M. Yen, C. Chin, H. C. Chung, H. C. Kuo, and H. H. Lin. 2007. Eosinophilic meningitis caused by *Angiostrongylus cantonensis* after ingestion of raw frogs. American Journal of Tropical Medicine and Hygiene 76:399–402.

Lunn, J. A., R. Lee, J. Smaller, B. M. MacKay, T. King, G. B. Hunt, P. Martin, M. B. Krockenberger, D. Spielman, and R. Malik. 2012. Twenty-two cases of canine neural angiostronglyosis in eastern Australia (2002–2005) and a review of the literature. Parasites & Vectors 5:1–18.

Ma, G., M. Dennis, K. Rose, D. Spratt, and D. Spielman. 2013. Tawny frogmouths and brush-tail possums as sentinels for *Angiostrongylus cantonensis*, the rat lungworm. Veterinary Parasitology 192:158–165.

Mackerras, M., and D. Sandars. 1955. The life history of the rat lung-worm, *Angiostrongylus cantonensis* (Chen) (Nematoda: Metastrongylidae). Australian Journal of Zoology 3:1–21.

Marsh, R. E. 1994. Roof rats. Pages B125–B132 *in* S. E. Hygnstrom, R. M. Timm, and G. E. Larson, editors. Prevention and control of wildlife damage. University of Nebraska Cooperative Extension, Lincoln, Nebraska, USA; U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Damage Control, Washington, D.C., USA; and Great Plains Agricultural Council, Wildlife Committee, Fort Collins, Colorado, USA.

Martin-Alonso, A., P. Foronda, M. A. Quispe-Ricalde, C. Feliu, and B. Valladares. 2011. Seroprevalence of *Angiostrongylus cantonensis* in wild rodents from the Canary Islands. PLOS ONE 6(11): e27747.

Monks, D. J., M. S. Carlisle, M. Carrigan, K. Rose, D. Spratt, A. Gallagher, and P. Prociv. 2005. *Angiostrongylus cantonensis* as a cause of cerebrospinal disease in a yellow-tailed black cockatoo (*Calyptorhynchus funereus*) and two tawny frogmouths (*Podargus strigoides*). Journal of Avian Medicine and Surgery 19:289–293.

New, D., M. Little, and J. Cross. 1995. *Angio-*

strongylus cantonensis infection from eating raw snails. New England Journal of Medicine 332:1105–1106.

Niebuhr, C. N., S. I. Jarvi, L. Kaluna, B. L. Torres Fischer, A. R. Deane, I. L. Leinbach, and S. R. Siers. 2020. Occurrence of rat lungworm (*Angiostrongylus cantonensis*) in invasive coqui frogs (*Eleutherodactylus coqui*) and other hosts in Hawaii. Journal of Wildlife Diseases 56: in press.

Nomura, S., and H. Lin. 1945. First case report of human infection with *Hemostrongylus ratti* Yokogawa. Taiwan No Ikai 3:589–592.

Prociv P., and M. Turner. 2018. Neuroangiostrongyliasis: the "subarachnoid phase" and its implications for anthelminthic therapy. American Journal of Tropical Medicine and Hygiene 98:353–359.

Qvarnstrom, Y., A. C. Aramburu da Silva, J. L. Teem, R. Hollingsworth, H. Bishop, C. Graeff-Teixeira, and A. J. da Silva. 2010. Improved molecular detection of *Angiostrongylus cantonensis* in mollusks and other environmental samples with a species-specific internal transcribed spacer based taqMan assay. Applied and Environmental Microbiology 76:5287–5289.

Qvarnstrom, Y., H. S. Bishop, and A. J. da Silva. 2013. Detection of rat lungworm in intermediate, definitive, and paratenic hosts obtained from environmental sources. Hawaii Journal of Medicine & Public Health 72:63–69.

Radomyos, P., A. Tungtrongchitr, R. Praewanich, P. Khewwatchan, T. Kantangkul, P. Junlananto, and S. I. Ayudhya. 1994. Occurrence of the infective stage of *Angiostrongylus cantonensis* in the yellow tree monitor (*Varanus bengalensis*) in five provinces of Thailand. Southeast Asian Journal of Tropical Medicine and Public Health 25:498–500.

Reddacliff, L. A., T. A. Bellamy, and W. J. Hartley. 1999. *Angiostrongylus cantonensis* infection in grey-headed fruit bats (*Pteropus poliocephalus*). Australian Veterinary Journal 77:466–468.

Richards, C. S., and J. W. Merritt. 1967. Studies on *Angiostrongylus cantonensis* in molluscan intermediate hosts. Journal of Parasitology 53:382–388.

Rosen, L., R. Chappell, G. L. Laqueur, G. D. Wallace, and P. P. Weinstein. 1962. Eosinophilic meningoencephalitis caused by a metastrongylid lung-worm of rats. Journal of the American Medical Association 179:620–624.

Rosen, L., G. Loison, J. Laigret, and G. D. Wallace. 1967. Studies on eosinophilic meningitis. 3. Epidemiologic and clinical observations on Pacific islands and the possible etiologic role of *Angiostrongylus cantonensis*. American Journal of Epidemiology 85:17–44.

Sawabe, K., and K. Makiya. 1995. Comparative infectivity and survival of first-stage larvae of *Angiostrongylus cantonensis* and *Angiostrongylus malaysiensis*. Journal of Parasitology 81:228–233.

Shiels, A. B., and W. C. Pitt. 2014. A review of invasive rodent (*Rattus* spp. and *Mus musculus*) diets on Pacific islands. Proceedings of the Vertebrate Pest Conference 26:161–165.

Shiels, A. B., W. C. Pitt, R. T. Sugihara, and G. W. Witmer. 2014. Biology and impacts of Pacific island invasive species. 11. *Rattus rattus*, the black rat (Rodentia: Muridae). Pacific Science 68:145–184.

Simões, R. O., A. Maldonado Júnior, N. Olifiers, J. S. Garcia, A. V. F. A. Bertolino, and J. L. Luque. 2014. A longitudinal study of *Angiostrongylus cantonensis* in an urban population of *Rattus norvegicus* in Brazil: the influences of seasonality and host features on the pattern of infection. Parasites & Vectors 7:1–8.

Spratt, D. M. 2015. Species of *Angiostrongylus* (Nematoda: Metastrongyloidea) in wildlife: a review. International Journal for Parasitology: Parasites and Wildlife 4:178–189.

Stockdale Walden, H. D., J. D. Slapcinsky, S. Roff, J. M. Calle, Z. D. Goodwin, J. Stern, R. Corlett, J. Conway, A. Mcintosh, J. Mendieta, Z. D. Goodwin, J. Stern, R. Corlett, J. Conway, and A. Mcintosh. 2017. Geographic distribution of *Angiostrongylus cantonensis* in wild rats (*Rattus rattus*) and terrestrial snails in Florida, USA. PLOS ONE 12(5): e0177910.

Stokes V. L., D. M. Spratt, P. B. Banks, R. P. Pech, and R. L. Williams. 2007. Occurrence of *Angiostrongylus* species (Nematoda) in populations of *Rattus rattus* and *Rattus fuscipes* in coastal forests of south-eastern Australia. Australian Journal of Zoology 55:177–184.

Timm, R. M., and R. Squill. 1994. Norway rats. Pages B105–B120 *in* S. E. Hygnstrom, R. M. Timm, and G. E. Larson, editors. Prevention and control of wildlife damage. University of Nebraska Cooperative Extension, Lincoln, Nebraska, USA; U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Damage Control, Washington, D.C., USA; and

Great Plains Agricultural Council, Wildlife Committee, Fort Collins, Colorado, USA.

Tobin, M. E. 1994. Polynesian rats. Pages B121–B124 *in* S. E. Hygnstrom, R. M. Timm, and G. E. Larson, editors. Prevention and control of wildlife damage. University of Nebraska Cooperative Extension, Lincoln, Nebraska, USA; U.S. Department of Agriculture, Animal and Plant Health Inspection Service, Animal Damage Control, Washington, D.C., USA; and Great Plains Agricultural Council, Wildlife Committee, Fort Collins, Colorado, USA.

Tomich, P. Q. 1969. Mammals in Hawaii. Bishop Museum Press, Honolulu, Hawaii, USA.

Wallace, G. D., and L. Rosen. 1965. Studies on eosinophilic meningitis. I. Observations on the geographic distribution of *Angiostrongylus cantonensis* in the Pacific area and its prevalence in wild rats. American Journal of Epidemiology 81:52–62.

Wallace, G. D., and L. Rosen. 1967. Studies on eosinophilic meningitis. IV. Experimental infection of fresh-water and marine fish with *Angiostrongylus cantonensis*. American Journal of Epidemiology 85:395–402.

Wang, L.-C., D. Chao, and E.-R. Chen. 1989. Acquired immunity in rats against *Angiostrongylus cantonensis* infection. International Journal for Parasitology 19:617–620.

Wang, Q. P., D. H. Lai, X. Q. Zhu, X. G. Chen, and Z. R. Lun. 2008. Human angiostrongyliasis. Lancet Infectious Diseases 8:621–630.

Wang H., L. Lu, D. She, Z. Wen, Z. Mo, J. Li, and H. Li. 2018. Eating centipedes can result in *Angiostrongylus cantonensis* infection: two case reports and pathogen investigation. American Journal of Tropical Medicine and Hygiene 99:743–748.

Wang, Q. P., Z. D. Wu, J. Wei, R. L. Owen, and Z. R. Lun. 2012. Human *Angiostrongylus cantonensis*: An update. European Journal of Clinical Microbiology and Infectious Diseases 31:389–395.

Wilmshurst, J. M., T. L. Hunt, C. P. Lipo, and A. J. Anderson. 2011. High-precision radiocarbon dating shows recent and rapid initial human colonization of East Polynesia. Proceedings of the National Academy of Sciences 108:1815–1820.

Yong, H. S., and P. Eamsobhana. 2013. Definitive rodent hosts of the rat lungworm *Angiostrongylus cantonensis*. Raffles Bulletin of Zoology 42:111–115.

Yong, W. K., and C. M. Dobson. 1982. The biology of *Angiostrongylus cantonensis* larvae in immune rats. Southeast Asian Journal of Tropical Medicine and Public Health 13:244–248.

York, E. M., C. J. Butler, and W. D. Lord. 2014. Global decline in suitable habitat for *Angiostrongylus* (= *Parastrongylus*) *cantonensis*: the role of climate change. PLOS ONE 9(8): e103831.

York, E. M., J. P. Creecy, W. D. Lord, and W. Caire. 2015. Geographic range expansion for the rat lungworm in North America. Emerging Infectious Diseases 21:1234–1236.

Zhang, R. L., M. X. Chen, S. T. Gao, Y. J. Geng, D. N. Huang, J. P. Liu, Y. L. Wu, and X. Q. Zhu. 2008. Enzootic angiostrongyliasis in Shenzhen, China. Emerging Infectious Diseases 14:1955–1956.

Associate Editor: S. Nicole Frey

CHRIS N. NIEBUHR is a research scientist for Manaaki Whenua – Landcare Research in Lincoln, New Zealand. As a vertebrate ecologist, he leads research efforts in conservation biology, invasive species management, and disease ecology in New Zealand and elsewhere in the Pacific. He received his B.S. degree with a double major in wildlife and fisheries sciences and entomology from Texas A&M University in College Station, Texas, USA, and his M.S. degree in wildlife management from Tarleton State University in Stephenville, Texas, USA. He earned his Ph.D. degree in zoology from the University of Otago in Dunedin, New Zealand, investigating transmission dynamics of avian malaria. As a postdoctoral research biologist for the U.S. Department of Agriculture National Wildlife Research Center Hawaii Field Station, his research focused on invasive rats and mongooses in island ecosystems. He continues to collaborate with researchers in Hawaii, Australia, and elsewhere on investigations into the epidemiology of rat lungworm disease.

SUSAN I. JARVI is a professor in the Department of Pharmaceutical Sciences at the Daniel K. Inouye College of Pharmacy at the University of Hawaii at Hilo. Her research interests include studies of infectious diseases such as avian malaria and avian pox, and more recently rat lungworm disease caused by the nematode Angiostrongylus cantonensis. She received her M.S. degree from the University of Massachusetts, Amherst; her Ph.D. degree from Northern Illinois University, DeKalb; and completed postdoctoral studies at the Beckman Research Institute at the City of Hope National Medical Center, Duarte, California, and the Molecular Genetics Lab at the Smithsonian Institution in Washington, D.C. In her current post, she has served as department chair of both biology and of pharmaceutical sciences.

SHANE R. SIERS is the island invasives project leader and field station leader at the U.S. Department of Agriculture National Wildlife Research Center (NWRC) Hawaii Field Station. He is a wildlife ecologist and conservation biologist working primarily on invasive vertebrates in island ecosystems (rodents, mongooses, reptiles, birds), particularly the notorious brown tree snake in Guam. After 6 years of active duty in the U.S. Marnie Corps and 10 years in the zoo field, from zookeeper to curator, he completed his B.S. degree in biology at the University of Massachusetts Boston, M.S. degree in biology (ecology, evolution and systematics) at the University of Missouri-St. Louis, and Ph.D. degree in ecology in the Colorado State University graduate degree program in ecology and Department of Fish, Wildlife, and Conservation Biology. He has worked in brown tree snake research since 2006, and as of October 2019 is being reassigned by NWRC to Guam to continue the fight.