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EVOLUTION OF THE COMMON BED BUG, CIMEX LECTULARIUS, IN THE URBAN ENVIRONMENT: FROM THE BIRTH OF CIVILIZATION TO GLOBAL DOMINANCE

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Abstract In recent years, urban evolutionary biology has emerged as a new and exciting field of study. Using genomic tools, it is now possible to investigate factors that influence demography, connectivity, and genomic diversity, to understand how organisms are adapting and evolving in response to the multitude of selective pressures that exist within cities and urban environments. The common bed bug, *Cimex lectularius* L., is proving to be an excellent model system with which to investigate urban evolution. It is a species with a long association with humans; the earliest records dating back to Pharaonic Egypt. Ancestrally, an ectoparasite of bats, a host transition to hominins occurred approximately 245,000 years ago, resulting in two extant lineages that do not appear to experience gene flow: one associated with bats and distributed across Europe and the Middle East, and the other with humans that now exhibits a near-global distribution. Despite the introduction of DDT in the 1940's, which single-handedly almost eliminated the species from modernized countries, populations of the human-associated lineage resistant to this and other broad-spectrum insecticides soon appeared and by the late 1990's the species was resurging across multiple continents at an alarming rate. Here, we discuss the evolutionary history of the common bed bug and the genetic characteristics of populations that have enabled it to become a prominent pest of the indoor environment.

Key Words: Cimicidae, Molecular markers, Insecticide resistance, Gene flow, Genetic diversity

INTRODUCTION

Over the last 30 years the common bed bug, *Cimex lectularius*, has re-emerged globally as a prominent pest of the indoor urban environment (Boase 2007; Potter et al. 2010). The origin for this resurgence is at present unknown; however, despite reports in the years proceeding World War II that suggested their effective eradication, records of infestations or methods of control across Europe, Asia, and Africa, can be found in the literature from the 1960s until the early stages of the resurgence, albeit in low numbers (Whitehead 1962; Cornwell 1974; Monov and Topalski. 1981); suggesting that eradication in these countries was incomplete. As such, it is likely that a combination of factors played a role in the species reemergence, including resurgence from local infestations in concert with introductions from distant and potentially international sources. Regardless of origin, the common bed bug is now established in most temperate regions around the globe (Zorrilla-Vaca et al. 2015) and reports of invasions into tropical regions are increasing (Cambronero-Heinrichs et al. 2020; Akhoundi et al. 2022).

In most countries where they occur, bed bugs are considered a pest of significance, impacting both physical and mental health (Doggett 2018a,b; Perron et al. 2018). Due to their blood feeding habits, several acute medical conditions may result. These include swellings and welts that can result in severe puritus and secondary infection (including bullous impetigo, *Staphylococcus aureaus* [MRSA]) (Goffard and De Shazo 2009; Loew and Romney 2011), the elicitation of immune responses that cause discomfort, and in extreme cases anaphylaxis (Klotz et al. 2009). Several disease-associated pathogens have also been isolated from bed bugs (e.g., Y. Pestis [Jordansky and Klodnitzky 1908], Hepatitis B [Blow et al. 2001], Trench fever [Leulmi et al. 2015]); however, there is no conclusive evidence that they are competent vectors to humans (Doggett 2018; Pietri 2020; Walt et al. 2024). The greatest concern, however, may result from the impact on an individual's mental health during or following infestations (Ashcroft et al. 2015) Impacts include shame, anxiety, social isolation, and stigma (Goddard and deShazon 2009), but may be as severe as post-traumatic stress disorders (PTSD) (Goddard and De Shazo 2012; Hwang et al. 2005). Individuals have reported psychological distress, nightmares, hypervigilance, insomnia, and personal dysfunction, and in extreme cases, paranoia, depression, suicidal thoughts/actions, and the need for medications and/or psychiatric counseling (Burrows et al. 2013; Perron et al. 2018). With the potential for the transmission of antibiotic-resistant microbes, a concern highly relevant in hospitals, assisted living facilities, and socio-economically depressed communities, and the significant mental health implications, the need to more completely understand the movement patterns and infestation dynamics of bed bugs has never been more relevant.

Since the dawn of civilization, bed bugs have played a role in human society (Panagiotakopulu and Buckland 1999; Potter et al. 2018). Despite a brief period of population decline following the introduction of synthetic insecticides in the late 1940's, they have returned to prominence to become a significant pest of the indoor urban environment. Within this, their strict association with humans has and will continue to influence their evolution as they respond to the urban-associated selection pressures to which they are exposed. Here, we will describe the bed bugs' rise to prominence, from the initial split from the ancient bat-associated lineage to their introduction into early civilized societies. Additionally, we will examine their patterns of spread, both local and long-distance, and the evolution of traits that promote success in the indoor urban environment; ending with a summary of the characteristics that make this a globally successful invasive species.

EVOLUTIONARY HISTORY AND HOST SPECIFICITY

While primarily associated with humans, the common bed bug evolved as an ectoparasite of bats ~ 2.5 million years ago (ya) (Roth et al. 2019), from which, based on molecular dating, a human-associated lineage emerged ~245,000 ya (Balvin et al. 2012). The date of this split potentially predates the movement of modern humans out of Africa, suggesting that the host transition may have occurred initially to hominins, possibly *Homo neanderthalensis*, and from there later to modern humans. Whereas the human-associated lineage has now spread to temperate regions around the globe, the bat-associated lineage persists in Europe, roosting in both caves and human-built structures (e.g., attics). No bat-associated *C. lectularius* populations have been reported in the U.S. Despite the potential for secondary contact between the contemporary populations of the human- and bat-associated lineage in Europe, gene flow between these appears absent (Booth et al. 2015; Balvin and Booth, 2018) (Fig 1.). This lack of contemporary gene flow is supported by nuclear genetic markers (Microsatellites [Booth et al. 2015] and single nucleotide polymorphisms [Miles et al. in review]), mitochondrial DNA (Balvin et al. 2012; Booth et al. 2015; DeVries et al. 2020), and knockdown resistance (*kdr*) associated mutations (Booth et al. 2015; Balvin and Booth 2019). Since expanding their host range to include humans, it is likely that bed bugs associated with hominins and early humans in caves, then propagules of the human-associated lineage were transported out of caves during the upper Paleolithic period as modern humans began to lead more nomadic lifestyles. This resulted in a genetic diversity of the human-associated lineage representing a subset of the overall genetic diversity found in the bat-associated lineage (Booth et al. 2015; Miles et al. in review). During the Last Glacial Maximum (LGM), both the bat- and human-associated lineages experienced population declines, as evidenced by reductions in effective population size (N_e) (Fig. 2). Whereas the human-associated lineage appears to have recovered and indeed overtaken ancestral estimates of N_e, the bat-associated lineage has continued to decline, likely due to habitat loss and host-population persecution.

Bed bugs have also been reported as a pest of significance in poultry farms (Axtell 1985; Szalanski 2018). Within this system, research has focused mainly on insecticide resistance and control (Steelman et al. 2008; González-Morales et al. 2022, 2023), while our understanding of the dynamics of invasion and spread are unknown. To our knowledge, no samples originating from poultry farms in Europe have been sequenced to determine the host-lineage to which they belong. Within the lab, the human-associated lineage feeds readily on chicken blood. Additionally, within the U.S., the common bed bug has been documented as a significant pest within poultry houses (Kulash and Maxwell 1945; Carter et al. 2011). Thus, we might predict that bed bugs within the poultry system in are of the human-associated lineage, with farm workers serving as vectors; as hypothesized for German cockroach, *Blattella germanica*, introductions into swine production facilities in the U.S. (Booth et al. 2011).

BED BUGS AND EARLY HUMAN CIVILIZATION

The indoor urban environment has clearly proven to be an ideal setting for the establishment and proliferation of bed bug populations. The earliest records of human-bed bug interactions date back ~3,575 years, with bed bugs remains found within a tomb in the workers village of Tell el-Amara (1352 – 1336 BC), Egypt. Prior to that, archeological remains are absent, however, evidence based on whole genome sequencing of the human-associated lineage of bed bugs suggest that an association with civilization occurred earlier than this. Based on changes in N_e, it appears that bed bugs likely were among the first urban insect pests to move with humans into the initial civilizations (Miles et al. in review). While the bat-associated lineage has continued to decline since the LGM, the human-associated lineage experienced an expansion starting at ~13,000 ya, then plateaued for ~5,000 years before experiencing a dramatic increase at ~7,000 ya, to present day values. Noteworthy dates here include the establishment of the first known city of Çatalhöyük, located in the southern Anatolia region of Turkey, ~10,000 ya, and the expansion of civilizations with the Cucuteni-Trypillia (~7,000 ya) and the Mesoptamians (~5,000 ya). Other commensal urban pests became associated with civilization much later (e.g., the German cockroach co-evolved with humans very recently, approximately 2,100 ya (Tang et al. 2024). Similarly, the black rat, *Rattus rattus*, is believed to have formed a commensal relationship with humans around 5,000 ya (Puckett et al. 2020). As civilization continued to expand, bed bugs moved also, with reports in Roman and Greek texts (Busvine 1976; Cowan 1865). Movement into Italy occurred by 77 CE, Germany by the 11th century, and France in the 13th Century

(Usinger 1966). Bed bugs were first reported in the UK in the 16th Century, then likely hitched their way to the U.S. on board ships carrying early European settlers (Marlatt 1916).

Insecticide resistance

Prior to World War II, bed bugs were a common indoor pest both in the U.S. and across Europe (Potter 2018). However, with the introduction of the organochlorine DDT for insect control in the mid 1940's, populations crashed, to the point that they were seemingly eradicated from modernized countries. However, within just a few years of its introduction, due to the evolution of mechanisms conferring insecticide resistance, reports of failure to control infestations began to arise (Johnson and Hill 1948; Busvine 1958; Whitehead 1962). Since then, insensitivity to other active ingredients, including organophosphates, carbamates, pyrethroids, neonicotinoids, and pyrroles, have been reported (Romero 2018). A diversity of mechanisms conferring resistance have evolved in bed bugs, including target-site mutations (e.g. *kdr* [Yoon et al. 2008], *Rdl* [Block et al. in review], increased metabolic detoxification (Romero et al. 2009; Adelman et al. 2011), cuticular penetration resistance (Koganemaru et al. 2013), and potentially behavioral resistance (Dang et al. 2017). Of these mechanisms, *kdr*-associated target site insensitivity to pyrethrin, pyrethroids, and organochlorides, has been extensively investigated. Resulting from point mutations in the voltage-gated sodium channel gene (Yoon et al. 2008), *kdr*-associated resistance is widespread (Booth 2024). To date, three *kdr*-associated mutations (V419L, L925I, I936F) have been linked to a reduction in sensitivity to pyrethroids (Yoon et al. 2008; Dang et al, 2015), and a fourth (F1524C) has been recently identified; however, its role in insensitivity is unknown (Porras-Villamil et al. 2025). The distribution and frequency of these mutations across the U.S., has significantly increased over the decade spanning 2008 - 2018 (Lewis et al. 2023), such that susceptible populations are no longer being detected (Holleman et al. 2018; Lewis et al. 2023). Interestingly, while two mutations predominate in the U.S. (V419L, L925I) (Lewis et al. 2023), the V419L mutation appears rare in Europe, the Middle East and Australia (Booth 2024).

In addition to *kdr*-associated insensitivity, the A302S resistance to dieldrin (*Rdl*) mutation has been detected in two populations in the U.S. (Block et al. in review). The *Rdl* mutation is linked to a reduction in sensitivity to phenylpyrazoles and cyclodienes in other insects (González-Morales et al. 2022). While resistance to the phenylpyrazole fipronil has been reported in *C. lectularius*, the A302S mutation was not detected in these populations (Gonzáles-Morales et al. 2021), hence research is required to assess whether resistance is conferred by this mutation. Additionally, the frequency and distribution of this mutation outside of the U.S. is at present unknown. Regardless, this finding represents the first record of a non-synonymous *Rdl* mutation in this species and identifies another mechanism by which insecticide resistance may be conferred in this species.

It is clear that bed bugs are rapidly evolving resistance mechanisms within the urban environment. That said, research is lacking as to the presence, frequency, and distribution of target-site mutations observed in other insects (e.g., nAChr and AChE). Similarly, while metabolic detoxification has been demonstrated, the regulatory mechanisms underlying these and their heritability are at present unknown.

Invasion dynamics and population structure from locale to broad scales

Since 2012, several studies have utilized microsatellite DNA markers in an attempted to elucidate patterns of genetic structure and gene flow among bed bug infestations (Booth et al. 2012; Saenz et al. 2012; Fountain et al. 2014; Akhoundi et al. 2015; Naran et al. 2015; Raab et al. 2016; Booth et al. 2018). These have provided some insight into the origin and spread of contemporary populations. For example, finding that gene-flow between the bat- and human-associated lineages of bed bugs in Europe is absent, rules out bat populations in urban areas as being a source for the current resurgence (Booth et al. 2015). Other studies have investigated the population genetics of regionally collected infestations and have found overall among-population levels of genetic diversity to be high (Saenz et al. 2012; Naran et al. 2015). However, the origin of individual infestations appears to be lone gravid females or small groups of highly related individuals (Booth et al. 2012; Saenz et al. 2012; Fountain et al. 2014; Akhoundi et al. 2015; Naran et al. 2015; Raab et al. 2016; Booth et al. 2018). Furthermore, among infestations gene flow appears to be absent (Saenz et al. 2012; Fountain et al. 2014), thus infestations grow through subsequent rounds of intensive inbreeding (Booth et al. 2012; Saenz et al. 2012; Fountain et al. 2014). The persistence under conditions of such limited within population genetic diversity suggests that bed bugs have purged deleterious alleles, resulting in a species ideally suited to the indoor urban environment.

Where these markers have failed, has been in the resolution of fine-scale structure, and hence community level infestation dynamics. This has been due to the limited level of resolution achievable even with large numbers of microsatellite markers, and the limited sample size screened in each study. Lewis (2024) addressed this knowledge gap hierarchically through genomic analyses of hundreds of bed bug populations using thousands of nuclear markers isolated through double-digest restriction-site associated DNA sequencing. At the national level, infestations within the U.S. exhibit an extensive hierarchy among samples, with genetic clusters evident both locally and nationally. Genetic differentiation among clusters was significant, as previously observed with microsatellite markers. At a regional scale, structure was evident within and among cities. Analysis of urban-suburban pairs within cities revealed that dispersal was primarily urban-urban or suburban-suburban. Where dispersal occurred between community types, it was mainly urban to suburban in direction. Bed bug population genetic structure was also assessed for association with different human-host characteristics. A non-random distribution of clusters across multiple socioeconomic and demographic variables was observed, providing support for the hypothesis of population structure driven by host population characteristics. Additionally, the presence of genetic clusters across multiple years suggests the presence of urban pest reservoirs within cities that contributes to local spread.

CONCLUSION

What is clear is that bed bugs share a long and close association with humans and human civilization. Demographic analysis suggests that they were likely one of *the* first urban pests in early civilizations. Over time, they spread to new regions as humans dispersed around the globe, such that by the 19th century, they were commonplace within urban centers. The introduction of synthetic insecticides such as DDT brought a rapid and widespread decline in populations; however, within a few years of their introduction resistance to these insecticides began to evolve. Populations were likely routinely suppressed as new active ingredients were introduced to the market, until by the late 1990's sufficient mechanisms had evolved to allow bed bugs to evade most insecticidal active ingredients currently in use. Between reemergence from local sources and introduction through national and internation travel, insecticide resistant bed bugs rapidly expanded their range, such that they are now found on all continents except Antarctica. Among populations genetic diversity is high, yet due to a lack of gene flow among populations, and the remarkable ability to resist the deleterious effects of inbreeding (Booth et al. 2012; Fountain et al. 2015), populations are founded by few individuals which rapidly establish, and unless eradicated become a source for subsequent infestations.

Reviewing the literature published over the last 15 years provides a hierarchical view of population structure, patterns of dispersal, and host-mediated selection in this significant urban pest insect. These studies may provide valuable information that may be used in the formulation of management strategies aimed at long-term control.

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