unique to the *Culex* genus, the 16.7 kD family, was previously discovered after salivary transcriptome analysis (*13*). The genome of *C. quinquefasciatus* revealed 28 additional members of this family.

We have outlined and quantified general similarity and differences at the chromosomal and genomic levels between three disease-vector mosquito genomes, building a foundation for more in-depth future analyses. We found substantial differences in the relative abundance of TE classes among the three mosquitoes with sequenced genomes. Most unexpectedly, this study revealed numerous instances of expansion of *C. quinquefasciatus* gene families compared with *An. gambiae* and the more closely related *Ae. aegypti*. The consequent diversity in many different genes may be an important factor that led to the wide geographic distribution of *C. quinquefasciatus*.

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Materials and Methods
Figs. S1 to S12
Tables S1 to S14
References

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Pathogenomics of *Culex quinquefasciatus* and Meta-Analysis of Infection Responses to Diverse Pathogens

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The mosquito *Culex quinquefasciatus* poses a substantial threat to human and veterinary health as a primary vector of West Nile virus (WNV), the filarial worm *Wuchereria bancrofti*, and an avian malaria parasite. Comparative phylogenomics revealed an expanded canonical *C. quinquefasciatus* immune gene repertoire compared with those of *Aedes aegypti* and *Anopheles gambiae*. Transcriptomic analysis of *C. quinquefasciatus* genes responsive to WNV, *W. bancrofti*, and non-native bacteria facilitated an unprecedented meta-analysis of 25 vector-pathogen interactions involving arboviruses, filarial worms, bacteria, and malaria parasites, revealing common and distinct responses to these pathogen types in three mosquito genera. Our findings provide support for the hypothesis that mosquito-borne pathogens have evolved to evade innate immune responses in three vector mosquito species of major medical importance.

The Southern house mosquito, *Culex quinquefasciatus*, is a geographically widespread, often abundant mosquito that is an epidemiologically important vector for an exceptionally diverse array of pathogens, including multiple arboviruses, filarial worms, and protozoa. *C. quinquefasciatus* transmits West Nile virus (WNV), St. Louis encephalitis virus, and other arboviruses, and acts as the most important vector of the causative agent of lymphatic filariasis, *Wuchereria bancrofti*, and *Plasmodium relictum*, an avian malaria parasite. Despite the public health importance of *C. quinquefasciatus*, knowledge of the insect's response capacities to this diverse array of pathogens is limited.

Availability of the *C. quinquefasciatus* genome sequence (*1*) enabled comparative phylogenomic analyses with *Aedes aegypti* (*2*), *Anopheles gambiae* (*3*), and *Drosophila melanogaster* (*4*) that identified 500 *C. quinquefasciatus* immunity genes from 39 (sub)families or processes (table S1). Conservation of *C. quinquefasciatus* gene family members follows the species phylogeny, showing greatest similarities with *A. aegypti*. Expansions of C-type lectins (CTLs), fibrinogen-related proteins (FREPs), and serine protease inhibitors (SRPNs) account for much of the 20 to 30% increase in *C. quinquefasciatus* immunity gene number compared with *A. aegypti* (417 genes) and *A. gambiae* (380 genes) (figs. S1 to S4). This apparent diversification in immune surveillance and immune signal amplification processes seems consistent with selection driven by polluted, microbially complex habitats in which *C. quinquefasciatus* oviposits and develops (*5*).

Whole genome microarray analysis revealed dynamic changes in infection response gene (IRG) transcription in WNV-infected mosquitoes (fig. S5). Significant changes are observed for 22 transcripts in the midgut and 309 in the carcass (i.e., the remainder of the body) at 7 days postinfection (dpi), with the greater number of IRGs in the latter apparently reflecting the diversity of infected cell and tissue types in the carcass. At 14 dpi, more IRGs are modulated in midgut (539) and carcass (490) when WNV infection has spread in midgut cells and has disseminated to the salivary glands (*6*). Few canonical immunity genes are represented among *C. quinquefasciatus* WNV IRGs (fig. S5). Five CTL genes within a *C. quinquefasciatus*–specific gene expansion (fig. S3) are up-regulated. Several genes related to the

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Toll, Imd, and JAK-STAT pathways, including *Spaetzle*, *REL1*, *IAP2*, and *STAT* orthologs, are activated in *C. quinquefasciatus* and in *A. aegypti* (*7*, *8*) by WNV and dengue virus (DENV) infection, respectively, further supporting a key role of these defense systems in controlling viral pathogens.

Although the *C. quinquefasciatus* genome encodes orthologs for all components of the antiviral defense RNA interference (RNAi) pathway (*9*), none of them is transcriptionally modulated significantly during WNV infection. Similarly, RNAi components are not transcriptionally modulated during arbovirus infection in *A. aegypti* (*10*), even though RNAi function is key to limiting these infections in mosquitoes (*10*–*12*). Apoptosis is evident, and *C. quinquefasciatus IAP1* is repressed in WNV-infected salivary glands (*6*, *13*). However, no significant changes in transcript abundance for caspases, caspase activators, *IAP* genes (other than *IAP2*), or autophagy-related genes are evident in WNV-infected *C. quinquefasciatus*, even though modulation of apoptosis (*14*) or autophagy (*15*) pathway function affects viral infection in flies. The nonresponsiveness of these genes appears to reflect the persistent and generally noncytolytic nature of arbovirus infections in a susceptible vector; overt activation of these responses would counteract virus persistence and transmission.

Comparative analysis of expressed sequence tags (tables S3 and S4) from *W. bancrofti*–infected *C. quinquefasciatus* revealed many novel IRGs, presumably because infection with a large metazoan parasite inflicts traumatic injury. Infection with non-native bacteria elicits acute cellular and humoral immune responses in *C. quinquefasciatus* and other vector mosquitoes (*16*–*18*). About 60% of *W. bancrofti* or bacteria IRGs are of diverse or unknown function (fig. S6), and only small proportions (4% *W. bancrofti* and 6% bacteria) are immunity genes. Comparison of *C. quinquefasciatus* virus, filarial worm, and bacteria IRGs reveals unexpected and extensive overlap (548 genes) between *W. bancrofti* and bacteria IRGs (Fig. 1A and fig. S6). Overall, 38 *C. quinquefasciatus* IRGs are common among all three infections (table S5).

The identification of *C. quinquefasciatus* IRGs provided an unprecedented opportunity to undertake a meta-analysis of 25 vector-pathogen interactions in *C. quinquefasciatus*, *A. aegypti*, and *A. gambiae* infected with arboviruses, parasites, and bacteria (Fig. 1B and table S6) within the context of orthologous groups (OGs) that define evolutionarily related genes. A set of 69 arbovirus IRG OGs (representing 93 *C. quinquefasciatus* and 89 *A. aegypti* genes) was implicated in *C. quinquefasciatus*–WNV, *A. aegypti*–DENV, and *A. aegypti*–Sindbis virus (SINV) responses (fig. S7 and table S7). A cytochrome P450 DENV IRG from *Drosophila* (*Cyp6a19*, FBgn0033979) and mammalian cells (*19*) is similar to genes that respond significantly in *C. quinquefasciatus–WNV* (CPIJ004411) infection and in *A. aegypti*–SINV and *A. aegypti*–DENV (AAEL009117) infections, highlighting the potential importance of this molecule as a universal arbovirus IRG. Filarial worm IRGs comprised 41 OGs modulated during *C. quinquefasciatus–W. bancrofti* infection and infection of *A. aegypti* with *Brugia malayi* (fig. S8 and table S8). The IRGs represented most frequently include serine proteases and cuticle proteins. Changes in the latter may be associated with tissue repair necessitated by parasite invasion, migration, and development (*20*). Increased representation of heat shock protein and cytochrome P450 IRGs appears to reflect stress during the infection response. The most extensive overlap (113 OGs) in bacterial IRGs was observed between Culicine mosquitoes, *C. quinquefasciatus*, and *A. aegypti* (table S9). Only 34 OGs and 26 OGs represent IRGs (fig. S9) in bacteria-infected *C. quinquefasciatus* and *A. gambiae* (table S10) and *A. aegypti* and *A. gambiae*, respectively. Among 16 OGs containing bacteria IRGs from all three species, serine proteases, cecropins, myosin light chain, and components of the 26S proteasome are highly represented (table S11). A meta-analysis of bacteria, filarial worm, virus, and malaria parasite infection data sets from *C. quinquefasciatus*, *A. aegypti*, and *A. gambiae* reveals 95 orthologous IRGs that span mosquito species and pathogen types (Fig. 1B, fig. S10, and table S12).

Orthology data (*21*) were employed to distinguish universal (see Fig. 1) multi- or single-copy OGs from mosquito-specific OGs, revealing that the majority of IRGs have orthologs across Arthropoda (Fig. 1C and table S13). Universal multicopy OGs are overrepresented among IRGs for viruses, filaria, and bacteria; and universal single-copy OGs are underrepresented among arbovirus and filarial worm IRGs (and among IRGs common to all pathogens in *C. quinquefasciatus*, *A. aegypti*, and *A. gambiae*) compared with the complete set of mosquito OGs (Fig. 1C). Immunity genes (IMM) (Fig. 1D), including CTLs, CLIPs, and SRPNs, are generally more prevalent among responsive multicopy OGs than among responsive single-copy OGs. In fact, no canonical immunity genes are found among arbovirus- or filarial worm–responsive universal single-copy OGs.

The cosmopolitan distribution of *C. quinquefasciatus* across continents and ecozones generally south of 39°N latitude implies that this species has the plasticity to adapt to diverse habitats, and this plasticity may be enhanced by an expanded immunity gene repertoire. Overrepresentation of universal multicopy OGs among pathogen IRGs implies that members of expanded gene families have been recruited into pathogen-responsive defense pathways. Arboviral and filarial worm infections constitute susceptible, long-term vector-pathogen interactions in which the pathogen undergoes amplification or develops intracellularly, whereas acute infections with non-native bacteria trigger systemic immunity and are cleared rapidly (*22*, *23*). Our meta-analysis reveals that arboviral and filarial worm pathogens transmitted by vector mosquitoes modulate very few canonical immunity genes and fail to affect expression of RNAi and most programmed cell death pathway genes in these vectors. Our results therefore provide strong support for the hypothesis that pathogens that successfully develop in, and are transmitted by, vector mosquitoes have

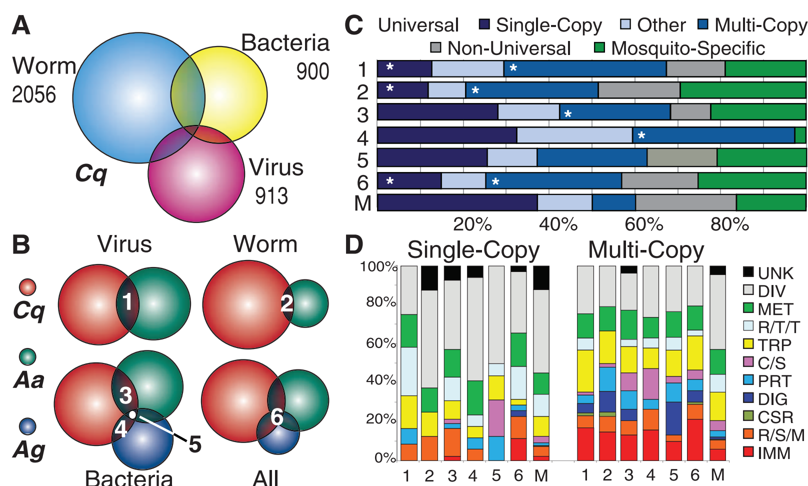

Fig. 1. Infection response genes (IRGs) in the mosquitoes *Culex quinquefasciatus* (*Cq*), *Aedes aegypti* (*Aa*), and *Anopheles gambiae* (*Ag*). (**A**) Shared and unique infection response genes in *C. quinquefasciatus* infected with a filarial worm, bacteria, or virus. (**B**) Proportions of shared and unique IRGs postinfection with viruses (1), filaria (2), or bacteria (3) in *C. quinquefasciatus* and *A. aegypti*, in *C. quinquefasciatus* and *A. gambiae* (4), and in all three species (5); and common IRGs in *C. quinquefasciatus*, *A. aegypti*, and *A. gambiae* (6). (**C**) Orthology relationships for IRG sets (Rows 1 to 6). IRGs with orthologs in at least 20 arthropod species were classified as Universal, as compared to Non-Universal or Mosquito-Specific. Gene copy–number counts distinguish mostly single- and multicopy orthologous groups. IRG sets 1 to 6 were compared to 10,083 mosquito OGs (Row M) to identify significantly greater or smaller (asterisks) proportions (Fisher's Exact Tests; $P < 1^{-5}$). (**D**) Consensus functional categories of universal single-copy (left) and multicopy (right) orthologous groups of IRG sets (Rows 1 to 6), and all mosquito groups (Row M). Functional groups are described in supporting online material and (*24*). Each set of IRGs is described in tables S7 to S12.

evolved to avoid most immune responses in the three mosquito genera responsible for the vast majority of human morbidity and mortality attributable to insect-transmitted pathogens.

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Materials and Methods
Figs. S1 to S12
Tables S1 to S13
References

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A Critical Role for LTA_4H in Limiting Chronic Pulmonary Neutrophilic Inflammation

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Leukotriene A_4 hydrolase (LTA_4H) is a proinflammatory enzyme that generates the inflammatory mediator leukotriene B_4 (LTB_4). LTA_4H also possesses aminopeptidase activity with unknown substrate and physiological importance; we identified the neutrophil chemoattractant proline-glycine-proline (PGP) as this physiological substrate. PGP is a biomarker for chronic obstructive pulmonary disease (COPD) and is implicated in neutrophil persistence in the lung. In acute neutrophil-driven inflammation, PGP was degraded by LTA_4H, which facilitated the resolution of inflammation. In contrast, cigarette smoke, a major risk factor for the development of COPD, selectively inhibited LTA_4H aminopeptidase activity, which led to the accumulation of PGP and neutrophils. These studies imply that therapeutic strategies inhibiting LTA_4H to prevent LTB_4 generation may not reduce neutrophil recruitment because of elevated levels of PGP.

Neutrophils are a critical component of the host's defense against microorganisms (*1*, *2*); however, cessation of neutrophil recruitment and clearance by apoptosis is mandatory to restore homeostasis and limit host tissue damage (*3*, *4*). Chronic neutrophilic inflammation is observed in lung diseases such as cystic fibrosis (CF) and chronic obstructive pulmonary disease (COPD), mediating extensive tissue damage and contributing to organ dysfunction (*5*, *6*). A classical chemoattractant for neutrophils is the glutamic acid–leucine–arginine (ELR^+) motif containing CXC chemokines (*7*), such as interleukin (IL)–8 (CXCL8) in humans and keratinocyte-derived chemokine (KC) (CXCL1) and macrophage inflammatory protein (MIP)–2 (CXCL2) in mice. Proline-glycine-proline (PGP) is a tripeptide generated from the breakdown of extracellular matrix collagen and is specifically chemotactic for neutrophils in vitro and in vivo (*8*, *9*). N-terminal acetylation of PGP (AcPGP), which occurs through an unknown mechanism, can enhance its chemotactic potential (*10*). PGP and AcPGP share sequence homology to key motifs found in the majority of ELR^+ CXC chemokines and bind to their receptors, CXCR1 and CXCR2 (*8*, *9*). PGP is generated from native collagen by the action of matrix metalloproteinase–8 (MMP-8) and/or MMP-9, followed by a secondary cleavage by prolyl endopeptidase (PE) (*9*). We have subsequently identified substantial quantities of PGP or AcPGP in clinical samples from patients with chronic lung diseases such as CF, COPD, and bronchiolitis obliterans syndrome (*8*, *9*, *11*, *12*), where it functions to promote the maintenance of neutrophilic inflammation at a time of declining classical chemokine levels. Here, we investigate the role of PGP in acute pulmonary neutrophilic inflammation.

Influenza infection of mice elicits an acute neutrophilic inflammation peaking at 24 hours post-infection (fig. S1, A and B) (*13*), coinciding with peak KC and MIP-2 levels (fig. S1, C and D). MMP-9 protein expression and activity were elevated at 24 hours post-infection and persisted for several days before subsiding to baseline levels (fig. S1, E to G). PE activity (fig. S1H) and protein amounts (fig. S1I) were also rapidly elevated in bronchoalveolar lavage fluid (BALF) after influenza infection, peaking at 24 hours after infection. Thus, the entire enzyme repertoire required for PGP generation was present. Neutrophils were demonstrated to be a prominent source of both MMP-9 and PE (fig. S1, J and K) (*13*). Despite the presence of MMP-9 and PE, however, no PGP was detectable at any time point that we analyzed (fig. S2A) with the use of a highly sensitive mass spectrometry technique (*8*).

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