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Leptospirosis, a spirochetal zoonosis, has spread from its traditional rural base to cause large epidemics in urban centres of developing countries. In the city of Salvador, we have shown that outbreaks occur each year during the same seasonal period of heavy rainfall and affect the same risk groups in poor urban slum communities. In Brazil alone, 10,000 cases of severe leptospirosis are reported annually during urban epidemics. Mortality among cases is >15%. Fiocruz-BA established R&D initiatives (Bio-Manguinhos and PDTIS) in 1999 to identify new strategies for intervention. These efforts have led to the sequencing of the genome of *Leptospira interrogans* serovar Copenhageni strain Fiocruz L1-130, the etiologic agent for urban epidemics, in collaboration with FAPESP. Data-mining of the genome identified 3,728 coding sequences, over 400 of which contain domains that maybe surface exposed. High-throughput expression and screening of these proteins identified a novel protein family of potential vaccine candidates as well as potential diagnostic markers for the disease. In addition, genome sequences are available for a closely related *L. interrogans* serovar Lai strain and two strains from the more distant *L. borgpetersenii*. Comparative genomics has revealed striking differences amongst these strains and will lead to new insights in understanding the pathology of *Leptospira* spp. and its interaction in the host.