Review

Urbanization and Vector-Borne Disease Emergence – a Possibility for Japanese Encephalitis Virus?

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Abstract | Population growth, urbanization and urban agriculture are three factors commonly quoted as important for disease emergence. Several of the mechanism by which urban disease emergence is promoted also increase the risks of vector-borne diseases, and the mosquito-borne Dengue virus is one of the pathogens benefitting from this. The related virus Japanese encephalitis virus is the most important cause of mosquito-borne encephalitis in the world, and is maintained in avian reservoirs and amplified by pigs. The occasional spill-over of the virus into humans results in more than 60 000 clinical cases of Japanese encephalitis annually, with high case fatality rates. The main vectors preferably feed on livestock and breed in rice fields, and the majority of cases subsequently occur in rural areas. This review lists the risks of emergence of diseases due to the on-going urbanization, with especial focus on vector-borne diseases, particularly Japanese encephalitis. It is concluded, that although the mechanisms required for an extensive human to human transmission is not present for Japanese encephalitis virus, there is evidence of urban virus transmission. Thus, considering increasing urbanization rates and intense contact between humans and pigs within the growing urban agriculture, there remains a risk for future emergence of Japanese encephalitis within cities as well as in rural areas.

Editor | Mohammad Ishtiaq Qadri, King Fahd Medical Research Center, King Abdul Aziz University, Saudi Arabia.
Received | **March** 13, 2014; **Accepted** | March 28, 2014; **Published** | April 7, 2014
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Citation | Lindahl, J. (2014). Urbanization and Vector-Borne Disease Emergence – a Possibility for Japanese Encephalitis Virus?. *British Journal of Virology,* 1(1): 10-20.

Introduction

During the last 50 years the human population has increased from three to seven billion, and this is estimated to further increase by some billions by 2050 (Bloom, 2011). Continuous with this population growth is an overall trend of urbanization, with an increase of the urban population with one million people every week (UN-habitat, 2004). The proportion of people living in cities recently exceeded 50% (Satterthwaite et al., 2010), and it is likely that by 2050, almost 70% will live in urban areas (Bloom, 2011). Asia is overall the most densely populated continent (Bloom, 2011), with more than half of the urban population of the world (Satterthwaite et al., 2010).

Simultaneously to the trends of population growth and urbanization, there are increasing numbers of events with emerging infectious diseases (Jones et al., 2008). Emerging infectious diseases are usually defined as diseases which are increasing in incidence in a population, or are spreading into new areas and new populations (Lederberg and Shope, 1992, Morse, 1995).

A majority of these diseases in humans are zoonotic, and the zoonotic diseases are more likely to be emerging than non-zoonotic (Taylor et al., 2000, Jones et al., 2008). Of all the emerging infectious disease events reviewed by Jones et al. (2008), 22.8% were vector borne, but during the last decade the proportion had increased to 28.8%. A number of anthropogenic factors are suggested drivers for the emergence of vector-borne as well as other infectious diseases, and urbanization is one of these (Patz et al., 2004) .

Japanese encephalitis virus (JEV) is the most important cause of vector-borne viral encephalitis in the parts of Asia where this flavivirus is transmitted (Mackenzie et al., 2004). It is estimated to cause more than 60 000 human cases annually (Campbell et al., 2011), and may have case fatalities of up to 50% in some outbreaks (Bista and Shrestha, 2005, Igarashi, 2002). Half of the survivors may have remaining sequelae after infection (Solomon et al., 2000, Halstead and Jacobson, 2003), which adds to the poverty promoting effect of disease (LaBeaud, 2008).

Japanese encephalitis virus is transmitted by mosquitoes between avian and porcine natural reservoirs with dead-end, spill-over transmissions to other vertebrates (Rosen, 1986, Erlanger et al., 2009). In addition to clinical disease in humans, horses may also develop clinical symptoms, including often fatal encephalitis, and pigs may abort or carry still-born piglets if they are infected during pregnancies (Calisher and Walton, 1996, Platt and Joo, 2006). The main vectors are culicine mosquitoes, whereof *Culex tritaeniorhynchus* is known to be the most important (Mackenzie et al., 2004), and breed to a large extent in rice fields in rural parts of South and East Asia (Rosen, 1986).

Whereas other vector-borne diseases have been emerging in urban areas, the extensive breeding of JEV vectors in rice paddies has kept JEV considered a rural disease. This review looks upon the urbanization process, the risks in cities of disease emergence generally and behind vector-borne diseases specifically. Thereafter the risk for JEV transmission in cities is further discussed.

Urbanization

There are multiple reasons behind the continuous urbanization process. Often the reason behind rural to urban migration is a hope of better jobs or lifestyle. It has in fact been shown that people in African cities are healthier than on the countryside (Hay et al., 2005), but statistics are seldom based on subdivision and the health situation is often worse in poorer areas (Moore et al., 2003). Informal settlements, or slum areas, can make up substantial parts of cities, for example, in 2001, 60% of urban inhabitants in Asia lived in slum areas (Mougeot, 2005).

Although rural-to urban migration often is caused by an urban pull, it may also be caused by a rural push. There may be continuous movements between peri-urban slums and rural areas, which increases the risks of disease transmission events (Wilson, 1995). Climate changes, disasters, war or political unrest can be causes of migrations and urbanisation (Wilson, 1995, Adamo, 2010).

However, not only urbanization is the reason why urban populations are increasing; cities can also have such a high reproduction rate that they would be growing even without inflow (Parnell and Walawege, 2011). All together the urban annual growth rate can be twice as high as the total population growth in a country (Donnelly et al., 2005).

Urban agriculture

Urban agriculture is most easily defined as agricultural activities in an urban area (Mougeot, 2000), although the definition of an urban area varies between countries and studies (Satterthwaite et al., 2010).

Urbanization creates needs and opportunities for urban food production, especially with growing demands for animal products (Yeung, 1988, Rae, 1998, Schiere and van der Hoek, 2001, van Veenhuizen and Danso, 2007). Urban agriculture often focus on special high value crop and perishable animal products giving high economical turnover from the limited area, and the scavenging behaviour of many animals, such as goats, poultry and pigs, make them suitable to keep without owning land (Schiere and van der Hoek, 2001, van Veenhuizen and Danso, 2007). These animals are also suitable in urban backyard production, since they require little space, reproduce quickly, and provide possibilities to use household wastes as feed.

Urban disease emergence

The main mechanisms by which urbanization promotes disease emergence is through increased population densities and bad sanitation, especially in low-income settlements (Lederberg and Shope, 1992) (Table 1). Even in Europe there is a trend of some diseases increasing in urban areas, such as parasitic larval

Table 1: *Factors contributing to urban disease emergence*

Factors contributing to urban disease emergence in general	Additional factors contributing to vector- borne disease emergence
• High population density • Urban agriculture • Aggregation of people from different areas • Presence of travel hubs, such as international airports • Influx of animals and animal-source food • Growing areas with poor standards (slums, informal settlements) and sanitation • Spatial restrictions forcing humans and animals closer together	• Decreased biodiversity • Increased temperatures • Reduced seasonal effects-prolonged breeding seasons • Increased water availability, year around • Provision of artificial containers, drains, sewage systems

migrans (Weaver et al., 2010). Increased travel and globalization are other factors important for transferring pathogens into naïve populations, and vice versa, and has been important for emergence throughout history (McMichael, 2002). As an example, between 1990 and 2007 international air arrivals in Asia increased from 56 to 184 million (Burchard et al., 2009) and in addition, millions of animals are transported both legally and illegally with only a small portion subjected to official disease control (Marano et al., 2007). Although these factors are not specific to urban disease transmission, most travel hubs are located in, or close to, urban areas.

Within the urban areas there are not only scavenging livestock. High densities of unwanted scavengers, including rats, increase the interface between humans and the urban wildlife, which may increase the incidence of leptospirosis (Kariv et al., 2001), bubonic plague (Stenseth et al., 2008) and other diseases.

Climate change may be a problem for diseases in urban areas, since it may increase urban flooding events, and in Africa many cities are situated so that a rise in water levels will cause serious flooding problems (Parnell and Walawege, 2011).

Urban emergence of vector-borne diseases

Vector-borne transmission is more complex than direct transmission of pathogens, which can make it difficult to predict how changes will affect the incidence. A basic feature of vector-borne transmission is that it is dependent on the vector capacity, defined as the number of bites that potentially could be infective that one individual will be exposed to during one day from one vector species (Cohuet et al., 2010, Black and Moore, 2005). The transmission is therefore primarily dependent on both the density and competence of present vectors, the density of susceptible hosts as well as density of amplifying hosts.

There is a large diversity of disease vectors, with different preferences as to breeding grounds, hosts and climatic requirements, and thus there is a risk that any ecological changes causes increased possibilities for some species. Most vectors show opportunistic feeding behaviour which causes them to change their feeding according to the host availability. Thus even mosquitoes with a strong preferences for humans will feed of other animals when they are abundant (Service, 1991), and vice versa. Many anthropophilic mosquitoes, including *Aedes albopictus* and *Culex quinquefasciatus* are prone to spread and invade new areas (Knudsen, 1995, Gratz, 2004, Hubalek, 2008, Miller et al., 1996). Increasing establishment of anthropophilic vectors, coupled with extensive urbanization in tropical regions, is suggested to be the future most important factor for arbovirus emergence (Saxena et al., 2011).

There are numerous ways in which urbanization may affect the transmission of vector-borne diseases. In and around cities there is a reduced biodiversity which means a lower number of alternate hosts that could add to a dilution effect, and thereby cause increased transmission to humans (Schmidt and Ostfeld, 2001, Bradley and Altizer, 2007, Keesing et al., 2010). The association is however not always straightforward. West Nile virus infection rates in mosquitoes has been shown to be increased with decreasing number of non-amplifying species, but the infection rate was also negatively correlated to increasing human population densities (Ezenwa et al., 2006). The movements of hosts in and out of cities can also be important for the epidemiology. After robins breed in urban sites, they disperse, and leave behind them infected vectors that need to shift hosts, and start feeding on humans (Kilpatrick et al., 2006).

Invertebrate vectors are depending on temperature for both pathogen reproduction in the vector and for vector behaviours and activity, such as feeding frequency and breeding. There is an increased temperature within and surrounding cities, which increase vector activity and also reduces seasonal effects (Shochat et al., 2006), enabling breeding for longer periods during the year.

Some vectors, such as *Cx. quinquefasciatus*, have a predilection for urban environments and will feed on humans indoors as well as outdoors (Sirivanakarn, 1976). This mosquito breeds in dirty water, and often breeds in latrines and artificial containers. The related Culex pipiens and Culex pipiens molestus also has a preference for urban areas (Epstein, 2001, Weitzel et al., 2011). Aedes aegypti is another anthropophilic mosquito which breeds in artificial containers and other water bodies present in urban and peri-urban areas. It has passed Ae. albopictus as the most important vector for Dengue virus in some areas, such as Vietnam (Huber et al., 2003). Where there is running water in cities, the mosquitoes become less depending on rainwater filling discarded garbage containers outdoor.

Dengue is the most prominent example where urbanization has played a major role in disease emergence, but also the exponential population growth that occurred after the Second World War, in association with unpreceeded globalization added to the rapid spread (Gubler, 2011). The four genotypes of the Dengue virus are estimated to infect up to 200 million humans per year, and the preference of the vector for humans enables the disease to spread and persist in large tropical cities, where millions of people live, the sheer number of households makes effective vector control nearly impossible, and the international airports nearby enables further spread (Gubler, 2011). Many other vector-borne viruses have sylvatic cycles but may anyway cause occasional urban outbreaks. One example is the Oropouche virus in South America (Pinheiro et al., 1981). In some areas, the deforestation and subsequent urbanization has been promoting emergence of Malaria and in sub-Saharan Africa, urban Malaria affects both capitals and medium sized towns (Donnelly et al., 2005) and 200 million urban inhabitants are estimated to be at risk (Keiser et al., 2004). Some African cities are also seeing increases in urban cases of Bancroftian filiariasis (Patz et al., 2005).

Japanese encephalitis virus and its vectors

Japanese encephalitis virus is maintained in nature in a cycle between birds, mainly ardeids, and culicide vectors, and pigs are the main amplifying hosts close to humans. Other vertebrates, such as bats (Kuno, 2001, Mackenzie et al., 2008), have been suggested to be important for the epidemiology, but, although possibly important for maintenance of the infection in areas where outbreaks are seasonal, will not be further considered here.

The most important vectors for JEV are in the *Culex sitiens* group, which are known for their preference to breed in rice fields, where the wading hosts often are present. This has caused JE to be considered a rural disease (Rosen, 1986, Endy and Nisalak, 2002, Balasegaram and Chandramohan, 2008), especially affecting communities with rice fields and pig keeping. The main factors attributed to the emergence of JEV are increases in rice and pig production that are on-going in many Asian countries (Erlanger et al., 2009).

However, JEV has been isolated from more than 25 species in the family Culicidae, and many of these species have also been shown to be able to transfer the virus to vertebrate hosts (Leake, 1992). The most important vectors for JEV are in the *Culex vishnui* subgroup of the *Cx. sitiens group, Cx. tritaeniorhynchus, Culex pseudovishnui* and *Culex vishnui* (syn. *Culex annulus*), and they are all zoophilic, feeding on cattle and pigs (Colless, 1959, Mitchell et al., 1973, Reuben et al., 1992b, Bhattacharyya et al., 1994, Arunachalam et al., 2004) depending on their availability, and only feed on humans in a limited extent. Of these vectors, *Cx. tritaeniorhynchus* was early shown to be highly competent (Gresser et al., 1958) and is often referred to as the most important vector (Mackenzie et al., 2004). Another vector in the *Cx. sitiens* group, *Culex annulirostris,* has been an important vector in the JE outbreaks in Oceania (Kramer and Ebel, 2003), and may locally feed up to 80% on feral pigs (Hall-Mendelin et al., 2012).

Different species in the *Cx. pipiens* complex are also competent vectors. *Culex quinquefasciatus (Culex pipiens quinquefasciatus*, syn. *Culex fatigans*, Southern house mosquito), common in tropical or subtropical regions (Sirivanakarn, 1976, Miller et al., 1996, Fonseca et al., 2004) was early shown to be able to transmit JEV, even after hibernation (Hurlbut, 1950). This is a highly anthropophilic species, with up to 50-76% feeding on humans (Reuben et al., 1992b, Zinser et al., 2004, Hasegawa et al., 2008). Also the anthropo

Table 2: *Culicide vectors for Japanese encephalitis virus*

Vector	Reported host preferences	Feeding on humans reported	Examples of breeding ground	Detected in urban/ suburban area
Culex vishnui subgroup[1]	Cattle, pigs	Yes	Rice fields, ditches, obstructed streams	Yes
Culex fuscocephala[2]	Cattle, pigs	Not shown*	Ponds, temporary water bodies, creeks	Yes
Culex gelidus[3]	Cattle, pigs	Yes	Deep water bodies, fish ponds, transient water pools	Yes
Culex bitaeniorhynchus[4]	Birds, humans, pigs	Yes	Swamps, rice fields, flooded stream beds	Yes
Culex quinquefasciatus[5]	Humans, birds	Yes	Sewers, drains, water containers	Yes
Culex annulirostris[6]	Marsupials, birds, domestic and feral pigs	Yes	Temporary water bodies	Yes

(Colless, 1959, Mitchell et al., 1973, Reuben et al., 1992b, Bhattacharyya et al., 1994, Arunachalam et al., 2005)
(Colless, 1959, Mitchell et al., 1973, Bhattacharyya et al., 1994, Arunachalam et al., 2005, Thein et al., 1988, Rueda, 2008) * No studies showing blood meals taken from humans found in this review.
(Reuben et al., 1992b, Hasegawa et al., 2008, Mwandawiro et al., 2000, Mwandawiro et al., 1999, Simpson et al., 1970, Whelan et al., 2000)
(Rueda, 2008, Reuben et al., 1992b, Reuben et al., 1992a, Dash et al., 2001)
(Reuben et al., 1992b, Hasegawa et al., 2008, Huber et al., 2002, Nitatpattana et al., 2005, Zinser et al., 2004)
(Hall-Mendelin et al., 2012, van den Hurk et al., 2001, Chapman et al., 2000, Le Flohic et al., 2013)

philic *Cx. pipiens molestus* is a competent vector for JEV (Turell et al., 2006, Olsen et al., 2010).

Other important zoophilic vectors are *Culex gelidus, Culex bitaeniorhynchus* and *Culex fuscocephala* (Colless, 1959, Reuben et al., 1992b). *Aedes albopictus* and *Ae. aegypti,* known for being important vectors for Dengue virus and Yellow fever virus, are experimentally competent vectors for JEV (Rosen, 1987, Rosen et al., 1985). The most important culicide vectors are listed in table 2.

Vector distribution is determined by the vectors' requirements for breeding grounds and preferences for blood meal hosts. However, although often located near preferred breeding sites, mosquitoes fly and can be easily dispersed by wind (Kay and Farrow, 2000, Wada et al., 1969), and therefore be found at a distance from expected sites.

Japanese encephalitis virus is present in South, East and Southeast Asia, pacific islands and Northern Oceania, an area where approximately three billion people live (Erlanger et al., 2009). Asia is also one of the most densely populated continents with 43% urban inhabitants in 2011, and 132 persons/km^2 (Bloom, 2011). If JEV would increase its transmission in urban areas, millions of people would be at increased risk.

Cx. tritaeniorhynchus, Cx. gelidus, and *Cx. quinquefasciatus* have been shown to be the most common mosquitoes found both in studies of an urban area in South India (Murty et al., 2010), and South Vietnam (Lindahl et al., 2012) (Table 2). In the latter study in Can Tho city, Vietnam, urban pig keeping was associated with increasing numbers of *Cx. tritaeniorhynchus,* and *Cx. gelidus*. The more anthropophilic *Cx. quinquefasciatus* was positively associated with the number of people in a household. The minimum infection rate in the urban mosquitoes was more than one per 1000 for both *Cx. tritaeniorhynchus* and *Cx. quinquefasciatus* and both JEV genotype I and III were found to be circulating in the same urban area (Lindahl et al., 2013). An earlier study in suburban Bangkok, Thailand, also detected JEV in *Cx. tritaeniorhynchus* and *Cx. gelidus* with minimum infection rates of 0.05 and 0.07 per 1000 mosquitoes respectively.

Table 3: *Differences in hosts and vectors between Dengue virus and Japanese encephalitis virus*

	Dengue virus	Japanese encephalitis virus
Amplifying hosts	Humans	Swine, birds
Main preference of the main vectors	Anthropophilic	Zoophilic, ornithophilic
Breeding preferences	Artificial containers	Natural water bodies with organic material

Seroconversion of humans in urban areas has also been demonstrated (Vallée et al., 2009). However, the mo-

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bile behaviour of humans makes it difficult to assess where the infection has taken place in many instances. Lindahl (2013) demonstrated JEV sero-conversion in pigs born within Can Tho city, Vietnam. Urban dogs have been demonstrated to be JEV sero-positive in Bangkok, Thailand, and it has been proposed that they could be good sentinels for JEV emergence (Shimoda et al., 2010, Shimoda et al., 2011, Shimoda et al., 2013).

Table 4: *Transmission of Japanese encephalitis virus and the factors influencing the transmission in rural, peri-urban and urban contexts*

	Rural	Peri-urban	Urban
Interface: Pigs-birds	High	Decreasing	Low
Interface: Humans-pigs	Depending on livestock system: Low to high	Depending on livestock system: Low to high	High
General Vector preferences	High zoophilic proportion	Decreasing zoophilic, increasing anthropophilic	High anthropophilic proportion
Vector larval habitats	High: Ponds, rice fields Low: Drains, sewers, artificial containers	Decreasing: Ponds, rice fields Increasing: Drains, sewers, artificial containers	Low: Ponds, rice fields High: Drains, sewers, artificial containers
Overall vector load	High	Decreasing	Low

As with other RNA viruses, the mutation rate is relatively high, but lower than for non-vector borne viruses (Jenkins et al., 2002, Holmes, 2004). Japanese encephalitis virus mainly evolve through this genetic drift (Halstead and Jacobson, 2003) but when different genotypes circulate in the same area, as may occur in a city (Lindahl et al., 2013), re-combinations can occur (Holmes, 2004, Twiddy and Holmes, 2003). There has, however, not been any report of JEV adapting genetically to the increased urbanization.

Conclusions

Urbanization can be a driver of emergence of diseases, and vector-borne diseases such as malaria and Dengue have been benefitting in some areas. Although both are mosquito-borne flaviviruses there are differences between Dengue and JEV (Table 3), the latter cannot be maintained in a cycle between humans using anthropogenic vectors. Infections in humans are the results of spill-over events from the transmission cycle between pigs and birds. However, it should be noted that the risk for JEV cannot be neglected in urban areas. Japanese encephalitis virus vectors have frequently been encountered in urban areas, the virus has been detected in urban centres and sero-conversion has been observed. There thus remains little doubt that urban transmission does occur.

Although the main vectors for JEV are zoophilic, anthropophilic vectors, such as *Ae aegypti*, *Ae albopictus* and *Cx. quinquefasciatus*, are well competent to transmit JEV, and could become of increased epidemiological importance in the future, with growing metropolitan areas. Co-circulation of JEV genotypes in urban areas could increase the risks for re-combinations that might be beneficial for enhanced spread.

The risk of spill-over events to humans are increased by a growing host animal population, and close contact with humans, assuming the presence of competent vectors (Table 4). The conclusion of this review is that with growing urbanization, accompanied by livestock and increased urban agriculture, there is a risk of growing numbers of urban JE cases, and an increased risk of adaptation of the virus to humans as well as to anthropophilic vectors.

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