

# **Emerging and re-emerging mosquito-borne infections: epidemiology and control from a modeling point of view**

## ***Infezioni emergenti e recidive dalle punture di zanzare: epidemiologia e controllo da un punto di vista modellistico***

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Infections transmitted by mosquitoes represent a significant fraction of disease burden worldwide and are emerging or re-emerging as an important threat to public health. Mosquito-borne diseases such as chikungunya and dengue are rapidly expanding their geographic range well beyond the tropical and subtropical belt. In Europe, the first recorded episode of chikungunya transmission occurred in Emilia Romagna, Italy, in 2007, and resulted in a large outbreak involving over 200 patients; in the summer of 2017, another outbreak of 400 cases originated in Anzio, involving neighboring cities including Rome, and seeding an additional outbreak of 100 cases in Guardavalle Marina, Calabria. Sporadic transmission of chikungunya has also been recorded in Southern France in 2010, 2014 and 2017. Dengue had also been absent from Europe since 1928 until the summer of 2010, when small outbreaks took place in France and Croatia. In 2012, the Portuguese island of Madeira witnessed a major outbreak with over 2000 cases; further sporadic cases of autochthonous dengue were more recently reported in France. Meanwhile, in the rest of the world, Zika has emerged as a new pandemic threat with severe congenital syndromes; outbreaks of Zika appeared in 2007 and 2014 in insular countries of the Pacific, then in 2015 it reached Brazil from which it spread explosively to most areas of Central and South America. Although Zika infection in humans is generally asymptomatic or very mild, it is capable of causing Guillain-Barre' syndrome in adults and congenital neuronal defects in newborns from mothers infected during pregnancy. Finally, large and deadly yellow fever outbreaks have occurred in Angola, Democratic Republic of Congo and Brazil since 2016, in spite of the major reductions achieved with the introduction of an effective vaccine since the '90s.

The growing role of mosquito-borne infection can be attributed to a number of factors. First, mosquitoes are increasingly becoming adapted to urban environments and colder climates, expanding their geographical range. *Aedes albopictus* was identified for the first time in Europe in Italy, in 1991; since then, it has rapidly expanded its habitat to temperate climates and it is now widespread in a large part of

southern Europe and the United States. *Aedes aegypti*, the main vector of chikungunya, dengue, Zika and yellow fever in tropical areas, has reappeared in isolated areas of Europe (the island of Madeira and areas around the Black Sea). Other invasive species, such as *Aedes koreicus* and *Aedes japonicus* are also establishing colonies in expanding areas of Northern Italy. Uncontrolled urbanization and the intensification of international travels and commerce are other factors that allow mosquito populations to spread globally and thrive locally; international mobility is also responsible for the importation of infected individuals from endemic countries to areas with suitable conditions for local transmission. More frequent viral transmission due to the shared habitat of humans and mosquitoes also imply higher probabilities for viruses to evolve mutations that allow them to increase their transmissibility. Finally, integrated vector management activities in endemic areas are often hampered by increasing rates of insecticide resistance, contributing to a resurgence of disease.

In this framework, mathematical and computational models can play an important role to assist public health systems and decision makers. The benefits of quantitative modeling can be grouped in three major areas: i) improve the basic knowledge on infection and outbreak dynamics, e.g. by identifying major drivers of transmission dynamics, estimating quantities that are difficult to measure, or ruling out hypotheses; ii) quantify potential transmission risks in unaffected areas or the potential burden of ongoing epidemics, providing critical information for resource allocation towards surveillance, response preparedness and control; iii) support the planning and design of preventive and reactive interventions by simulating alternative scenarios and gauging the effect of potential uncertainties. In this presentation, we will showcase a number of practical applications of models to the vector population, behavior and ecology, allowing the estimation of potential transmission risks to

humans and the cost-effectiveness of preventive interventions. We will then proceed to illustrate multiple examples in which models have allowed the quantitative inference of actual outbreak dynamics for chikungunya, dengue and Zika.

A key indicator of the transmission risk for infectious diseases is the basic reproduction number  $R_0$ . In the case of mosquito-borne infections,  $R_0$  is directly proportional to the ratio between the density of mosquitoes and the density of humans in a given area; other factors determining  $R_0$  include characteristics of the infectious disease (incubation periods in humans and mosquitoes, duration of the infectious period), the ability of mosquitoes to transmit the virus (called vector competence), and the mosquito biting rate. If sufficient knowledge on the natural history of disease and on the competence of mosquito species for a given virus is available, the risk of transmission in a given area can be estimated by inferring the temporal evolution of the mosquito abundance.

To estimate transmission risks of tropical diseases in Italy, we developed a mathematical model representing the dynamics of *Aedes albopictus* populations throughout the whole developmental cycle (eggs, larvae, pupae, female adults); previous estimates of temperature-dependent rates of mortality, development from one stage to the next, and gonotrophic cycle were based on publicly available

experimental data. The model was fitted to capture data from ten municipalities in the provinces of Trento and Belluno across the mosquito seasons of 2014 and 2015. We found a significant risk of chikungunya outbreaks in most sites if a case was imported from endemic areas between the beginning of summer and up to mid-November, with an average outbreak probability between 4.9% and 25%, depending on the site. A lower risk was predicted for dengue, with an average probability between 4.2% and 10.8% in a restricted window of importation (between mid-July and mid-September). We later used the same estimates on mosquito abundance to provide a timely risk assessment during the Zika pandemics in 2016, highlighting a consistently low risk of autochthonous mosquito-borne transmission in Northern Italy, as long as the vector competence of *Aedes albopictus* remains at the currently measured levels.

In a separate study, we then moved on from the simple assessment of transmission probabilities to estimate the potential size of chikungunya and dengue outbreaks by means of a stochastic transmission model. We also evaluated the ability of preventive approaches to reduce vector populations and consequently transmission risk and outbreak sizes and we analyzed its cost-effectiveness. The vector population model was modified to include routine larviciding and different scenarios were analyzed in terms of the timing of the intervention and on the areas treated (i.e., public spaces or including private premises). The model was parametrized using data from pilot studies on the use of larvicides in public and private premises in the same setting where mosquito capture data had been collected. We found that routine larviciding of public catch basins can limit both the risk of autochthonous transmission and the size of potential epidemics. Ideal larvicide interventions should be timed in such a way to cover the month of July. Optimally timed larviciding can reduce locally transmitted cases of chikungunya by 20%-33% for a single application (dengue: 18-22%) and up to 43%-65% if treatment is repeated four times throughout the season (dengue: 31-51%). In larger municipalities (>35,000 inhabitants), the cost of comprehensive larviciding over the whole urban area overcomes potential health benefits related to preventing cases of disease, suggesting the adoption of more localized interventions. Small/medium sized towns with high mosquito abundance will likely have a positive cost-benefit balance. Involvement of private citizens in routine larviciding activities further reduces transmission risks but with disproportionate costs of intervention.

A similar approach to studies presented until now was applied to analyze in real-time an actual, rather than potential outbreak, namely the 2017 chikungunya outbreak in Anzio. Using entomological capture data collected in 2012 from 18 sites along a 70 km-transect from the Lazio coast (four sites) to rural inland areas, and temperature data from 2017, we estimated the mosquito population densities. We coupled these estimates with data on human landing captures to estimate the mosquito biting rate and computed the probability of outbreak and outbreak size for different time of the year in the region. We found that the index case was likely introduced in the first week of June in Anzio (range: 21 May-18 June)

and in early July in Rome (range: 28 May-16 July). We estimated a higher risk of large outbreaks in coastal and rural sites than in urban sites, despite the high vector abundance in some urban areas, and a significant probability of observing additional

transmission up to mid-November (later confirmed by observations). We also estimated the probability that one blood sample might have been collected from an infected individual to be about 0.73% (95% CI: 0.28–1.34%) in Anzio and 0.15% (95% CI: 0.05–0.29%) in Rome. Based on average costs and Disability Adjusted Life Years (DALY) lost per observed symptomatic chikungunya case, we estimated a total economic burden for the outbreak in Lazio at 322,000 EUR (95% CI: 222,000–477,000) with a loss of 341 DALYs (95% CI: 235–505) (excluding costs related to the management of blood supplies after restrictions and cases from the related outbreak in Calabria).

In another analysis, we investigated the transmission dynamics of the first Zika outbreak in the United States in Miami, during the summer of 2016, using a mathematical model calibrated to observed data on mosquito abundance and symptomatic human infections. We found that, although Zika transmission was detected in July 2016, the first importation may have occurred between March and mid-April. The estimated peak value for  $R_0$  was 2.73 (95% CI: 1.65–4.17) and the attack rate was 14% (95% CI: 5.6–27.4%), with 15 (95% CI: 6–29) pregnant women involved and a 12% probability of infected blood donations. We estimated that vector control allowed to curb the outbreak, avoiding 60% of potential infections. We also demonstrated that further Zika outbreaks identified in other areas of Miami later in the year were likely seeded by commuters rather than by further importation from international travelers.

Finally, we used a completely different approach to quantitate the spatiotemporal spread of dengue, using Bayesian inference of transmission chains on data from four epidemiological years in Porto Alegre, a non-endemic metropolitan city in Latin America. We found that transmission clusters expanded by linearly increasing their diameter with time, with an average rate of about 600m/month. The large majority (70.4%, 95%CI: 58.2–79.8%) of individual transmission events occurred within a distance of 500m. The cluster diameter,

duration and epidemic size were proportionally smaller when control interventions were more timely and intense. Results suggested a large proportion of cases to be transmitted via short-distance human movement (<1km) and a limited contribution of long-distance commuting within the city. This information was then used to build a stochastic model of spatio-temporal disease transmission to evaluate the impact of Ultra-Low-Volume insecticide spraying on the prevention of dengue cases. We found an ULV-induced mortality of 30% for mosquitoes and that the implemented control interventions avoided about 33% of symptomatic cases occurred in the area. We show that increasing the radius of treatment or the mortality of mosquitoes by treating gardens and/or indoor premises would greatly improve the result of control, but with important trade-offs with respect to the need for increased resources.

These applications elucidate the different ways in which data-driven modeling can contribute to decision making in public health, in order to face the growing threats of mosquito-borne infections. The extraction of valuable information hidden in the data is critical for preparedness and optimal resource assessment both during ongoing outbreaks and in time of peace.