STUDY DESIGN ARTICLE

COACTION PUBLISHING

DengueTools: innovative tools and strategies for the surveillance and control of dengue

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Dengue fever is a mosquito-borne viral disease estimated to cause about 230 million infections worldwide every year, of which 25,000 are fatal. Global incidence has risen rapidly in recent decades with some 3.6 billion people, over half of the world's population, now at risk, mainly in urban centres of the tropics and subtropics. Demographic and societal changes, in particular urbanization, globalization, and increased international travel, are major contributors to the rise in incidence and geographic expansion of dengue infections. Major research gaps continue to hamper the control of dengue. The European Commission launched a call under the 7th Framework Programme with the title of 'Comprehensive control of Dengue fever under changing climatic conditions'. Fourteen partners from several countries in Europe, Asia, and South America formed a consortium named 'DengueTools' to respond to the call to achieve better diagnosis, surveillance, prevention, and predictive models and improve our understanding of the spread of dengue to previously uninfected regions (including Europe) in the context of globalization and climate change.

The consortium comprises 12 work packages to address a set of research questions in three areas:

Research area 1: Develop a comprehensive early warning and surveillance system that has predictive capability for epidemic dengue and benefits from novel tools for laboratory diagnosis and vector monitoring.

Research area 2: Develop novel strategies to prevent dengue in children.

Research area 3: Understand and predict the risk of global spread of dengue, in particular the risk of introduction and establishment in Europe, within the context of parameters of vectorial capacity, global mobility, and climate change.

In this paper, we report on the rationale and specific study objectives of 'DengueTools'. DengueTools is funded under the Health theme of the Seventh Framework Programme of the European Community, Grant Agreement Number: 282589 Dengue Tools.

Keywords: *dengue*; *dengue control*; *dengue diagnostics*; *economic evaluation*; *entomology*; *climate change*; *early warning systems*; *risk mapping*; *surveillance*; *globalization*

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Dengue is the most important arboviral disease of humans (1). Global incidence has risen rapidly in recent decades. Some 3.6 billion people, half of the world's population, are now at risk, mainly in the urban centers of the tropics and subtropics (1, 2). Global reports of dengue hemorrhagic fever (DHF) have increased by fivefold in the past 20 years. The World Health Organization (WHO) estimates that there are 50–100 million infections worldwide every year, of which 21,000 are fatal (3). However, these numbers are gross underestimates since recent studies suggest that the figures are much higher, with as many as 230 million infections, tens of millions of cases of dengue fever (DF), and millions of cases of DHF (2, 4–6). The disease is now endemic in more than 100 countries in Asia, Africa, and the Americas. The Asia-Pacific region is the most seriously affected, with increasing number and magnitude of dengue epidemics and expanding geographical distribution (7). Dengue inflicts a significant health, economic, and social burden on the populations of endemic areas. The number of disability-adjusted life years (DALYs) worldwide is estimated to range between 528 and 621 per million population (8). There is no specific treatment for dengue, but appropriate medical care can save the lives of patients with DHF.

There are four antigenically distinct dengue viruses belonging to the genus *Flavivirus* of the family Flaviviridae. Infection with one serotype confers long-term immunity to that serotype but not to the others. The strain of virus, secondary infection, age, and host genetics are the most important risk factors for severe disease, although the pathogenetic mechanisms remain poorly understood (8).

Dengue viruses are transmitted by mosquitoes of the genus *Aedes*, subgenus *Stegomyia*. The principal vector, *Aedes Stegomyia aegypti*, is now well established in much of the tropical and subtropical world, particularly in urban areas. It is a domestic species, highly susceptible to dengue virus infection, feeding preferentially on human blood during the daytime often taking multiple blood meals during a single gonotrophic cycle (8). It typically breeds in clean stagnant water in artificial containers and is, therefore, well adapted to urban life. A second species, *Aedes Stegoymyia albopictus*, is generally considered a less-effective epidemic vector because, unlike *A. aegypti*, it feeds on many animals other than humans and is less tied to the domestic environment (9). Nevertheless, this species has transmitted small outbreaks in some regions, and in recent years, its importance has increased because of its rapidly expanding range due to global commerce in used tyres and other containers (10).

Current surveillance systems and control strategies are clearly insufficient to prevent epidemic dengue in endemic countries or to prevent its introduction into uninfested regions (including Europe) (11). For this reason, in 2010, the European Commission announced a funding call for the 7th Framework (Box 1). Within this call, we have focused on better diagnostics, surveillance, and prediction of dengue introduction into currently uninfected regions.

We formed a consortium of 14 partners based in South East Asia, South Asia, South America, and various centers in Europe (Fig. 1). Led and hosted by the University of Umeå in Sweden, the consortium includes partners from academic institutions, the Ministry of Health in Sri Lanka, a research-intensive small to middle size research enterprise (SME), and two research companies. Experts in this consortium include physicians, epidemiologists, mathematical modellers, climate experts, environmental scientists, laboratories, ecologists, chemical ecologists, entomologists, and a health economist

Box 1: European Commission, Seventh Framework programme, FP7 Cooperation – Health

HEALTH.2011.2.3.3-2: Comprehensive control of dengue fever under changing climatic conditions. FP7-HEALTH-2011-single-stage.

Research should develop innovative tools for one or more of the following aspects: better diagnosis, surveillance, development of treatment, prevention and vaccination strategies, prevention, and/or prediction and prevention of the spread of dengue fever to previously uninfected regions (including Europe), in the context of climate change. Research may also include studies on the underlying pathogenesis with respect to viral and host factors that can predict disease severity and prepare for further development of new vaccines, antiviral compounds, and more targeted treatment schemes.

Funding scheme: Specific International Cooperation Action (SICA) Collaborative Project (small- or medium-scale focused research project) target regions: Latin America and/or Asia. SICA aims to bring about the balanced participation of third countries in collaboration with European partners.

Expected impact: Better tools, and the use thereof, for improved comprehensive control of dengue fever at a global level. Participation from both SICA target regions and SMEs in the projects should help ensuring innovation and exploitation of the results in this area/topic. The degree of such participation will be considered during the evaluation.

Source: http://ec.europa.eu/research/health/infectious-diseases/emerging-epidemics/call-for-proposals_en.html

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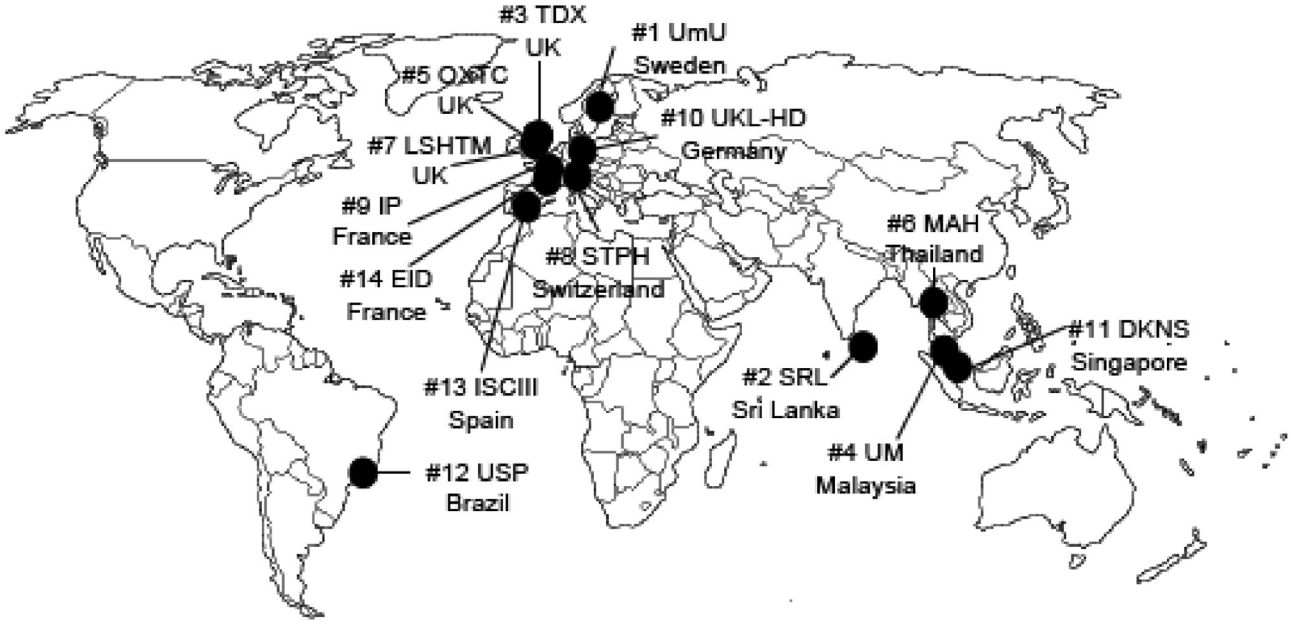

Fig. 1. Geographic distribution of the 14 DengueTools consortium partners.

(Table 1). The strength of the consortium lies in the breadth of expertise and the international network of partners from which it draws to address the challenging tasks of the 7th European Union Framework. The acronym of our 4-year project is 'DengueTools'.

Rationale and research objectives

DengueTools created 12 work packages (Fig. 2) to address gaps related to (1) surveillance, (2) control, and (3) risk of introduction of dengue to uninfected areas.

Table 1. Integrated expertise of members the consortium

Expertise	Partner												
	1Umeå, Sweden	2 Colombo, SriLanka	3 Cambridge, United Kingdom	4 Kuala Lumpur, Malaysia	5 Oxford, United Kingdom	6 Bangkok, Thailand	7 London, United Kingdom	8 Basel, Switzerland	9 Paris, France	10 Heidelberg, Germany	11 Singapore, Singapore	12 São Paulo, Brazil	13 Madrid, Spain	14 Montpellier, France
Data management + population studies	✓													
Disease surveillance		✓						✓			✓			
Entomology		✓			✓	✓	✓		✓		✓			✓
Vector control							✓		✓					✓
GIS and remote sensing										✓				
Climate change	✓									✓				
Modeling	✓									✓		✓		
Clinical/community trials	✓					✓								
Clinical management		✓						✓						
Viral genetic studies		✓									✓		✓	
Diagnostic assays			✓	✓							✓			

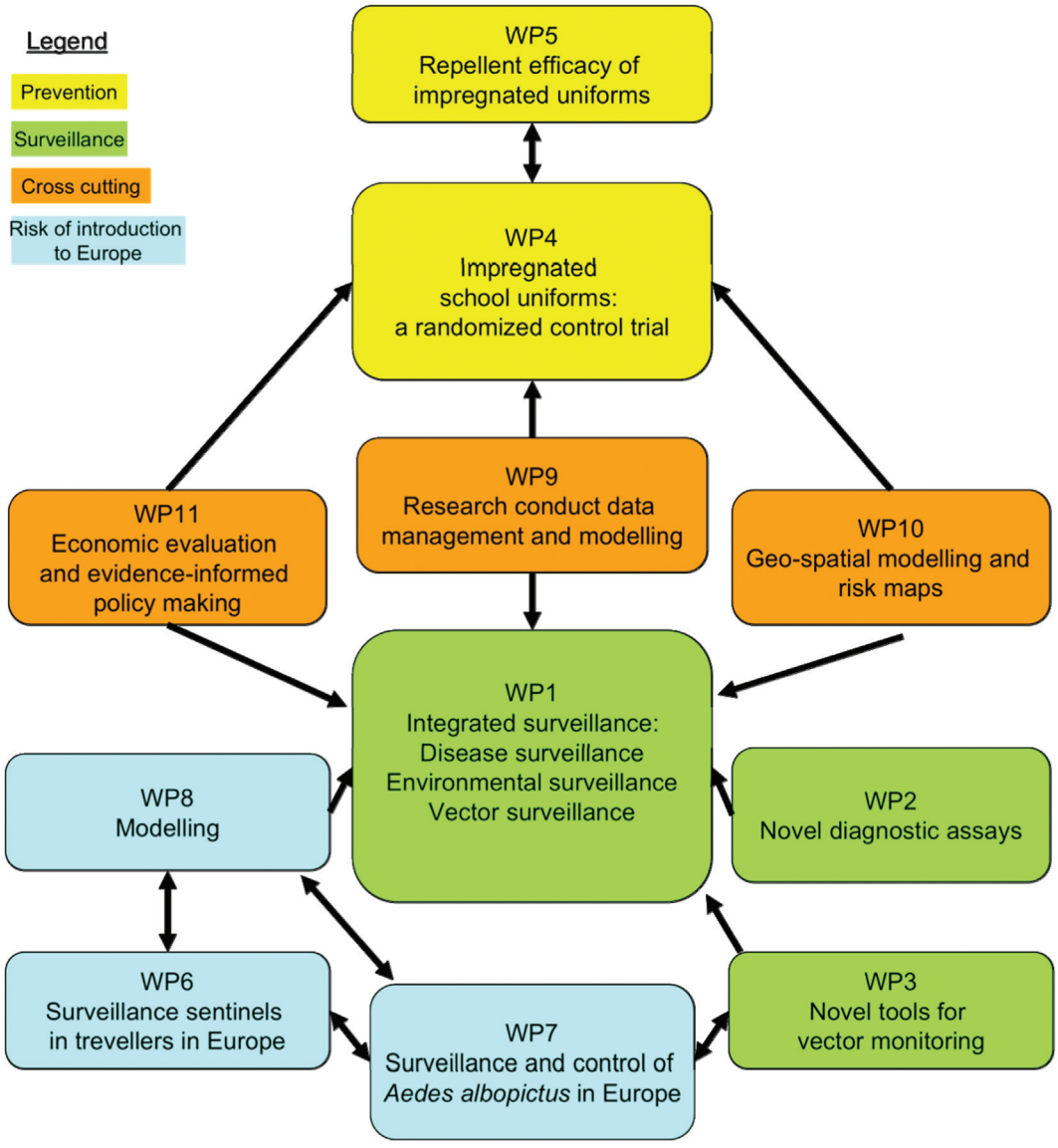

Fig. 2. Twelve work packages (WP) and their interconnectedness around the three research areas. Work package 12 handles the management and dissemination of all work packages (not included in this figure).

Research gaps identified in these three research areas are summarized in Box 2.

Research area 1

Main research objective

Develop a comprehensive early warning surveillance system that has predictive capability for epidemic dengue using novel tools for laboratory diagnosis and vector monitoring.

Rationale

The dramatic global spread and increased frequency and magnitude of epidemic DF/DHF in the past 40 years underscore the critical need for more effective surveillance, prevention, and control of this disease. Most endemic countries do not have adequate surveillance to monitor dengue disease. The main purpose of surveillance is to provide information on risk assessment, epidemic response, and programme evaluation and to allow timely action to prevent or control dengue epidemic.

The risk of epidemic dengue transmission is determined by a combination of factors that include the level of herd immunity to virus serotypes; virulence characteristics of the virus strain; survival, feeding behavior, and abundance of *Aedes* mosquitoes; weather; and socioeconomic factors and human population density, distribution, and movement (12). Several potential predictive indicators for outbreaks have been described but require further study (13, 14).

The appearance of a new dengue serotype can be used as an early warning sign, although it does not always predict the occurrence of an immediate epidemic (15).

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Box 2: Research gaps identified by the DengueTools consortium

Gaps in dengue surveillance:

1. Lack of understanding of individual or combined roles of viral, entomological, ecological, environmental, and climate factors that influence dengue transmission dynamics and their respective outbreak predictive capability
2. Lack of evidence on the most feasible, sustainable, and cost-effective approach to integrated surveillance
3. Lack of sensitive and specific early diagnostic assays for field use (inexpensive, rapid results, point-of-care, and portable)
4. Lack of sensitive, reliable, and simple field methods for vector surveillance

Gaps in the prevention and control of dengue:

1. Lack of effective control strategies to protect children
2. Lack of evaluation of current control methods of vectors, in particular the differences in the control of *A. aegypti* and *A. albopictus*, which have implications for vector control efforts in Europe.

Gaps in understanding the risk of introduction of dengue to non-infected areas, including Europe:

1. Insufficient data on the magnitude and trends of importation and virus evolution over time and by geographic origin
2. Poor understanding of vector density, preferred breeding sites, and vectorial capacity of vectors in temperate climates that are needed for predictive models under changing climate conditions
3. Lack of predictive models for the risk of establishment of dengue in uninfected regions (in particular Europe), taking into account global travel networks and climate change

The association between the introduction of a new serotype and outbreak occurrence remain unknown but the time lag may vary from 1 to 2 months to years.

The evolution of dengue viruses may have a major impact on their epidemic potential, virulence for humans, and geographic spread around the world (16). Currently, dengue viruses can be classified as being of epidemiologically low, medium, or high impact; i.e. some viruses may remain in sylvatic cycles with little or no transmissibility to humans; others are associated with DF only, and some strains have the potential to cause major epidemics and more severe DHF and DSS (16–18). Phylogenetic and epidemiological analyses suggest that the genotypes and subtypes with greater epidemic potential regularly displace those that have lower epidemic potential. Nevertheless, a more complete understanding of the evolution and epidemiology of dengue viruses, particularly with respect to predicting epidemics of more severe disease, requires large-scale prospective studies that compare phenotypic expression with genetic changes in the viruses (18, 19).

The major components of dengue surveillance include monitoring the disease, mosquito vectors, and environmental and social risks (3). A Cochrane review of the application of tools for dengue outbreak prediction/detection and trend monitoring in surveillance systems highlighted the lack of evidence on the most feasible and sustainable surveillance approach (14). Prospective studies are needed to better define the most appropriate and cost-effective dengue surveillance system and to identify triggers for dengue emergency response. For surveillance to effectively provide early warning for epidemic transmission, it must be active, laboratory based, and comprehensive in its coverage of the spectrum of clinical illness, the catchment area, and the factors that influence transmission dynamics. We propose to study individual and combined indicators for outbreak detection and prediction to assess the relative value of each. Particular attention will be given to the role of viral factors. These data will be used to develop models capable of predicting epidemics, thereby providing more precise information on risk areas to target control activities.

Finally, given the limited resources in most dengue endemic countries, it is crucial to identify the most sensitive, specific, and cost-effective signal or combination of signals for an early warning system that would allow timely institution of control measures. Our consortium will address the affordability and sustainability of an active sentinel surveillance system, an important issue for policy makers.

Diagnostic assays

The lack of laboratory capacity and capability and the availability of affordable, sensitive, and specific diagnostics contribute to the poor surveillance in resource-limited countries. Accurate laboratory diagnosis of dengue patients is important to the individual patient and for surveillance and control efforts. An accurate point-of-care diagnosis can assist in patient management, prevent unnecessary and possibly expensive antibiotic usage, facilitate triage of febrile patients into appropriate clinics, and reduce health care utilization costs. We propose to develop two potential diagnostic assays, by using the recombinase polymerase amplification technology and the loop-mediated isothermal amplification approach.

Furthermore, new rapid, inexpensive, and operationally amenable methodologies are needed for vector

surveillance. We propose to develop novel tools for vector monitoring, including the use of attractants to increase trap efficacy in the field. Available adult traps vary in cost, species-specificity, and capture rate. For example, BG-Sentinel traps are expensive and require electrical power, which restrict the number of such traps than can be deployed. Different applications may have different requirements in terms of preferred specificity for different mosquito species, or even sex or age of mosquitoes within a given species; so, there may not be one optimal trap for all purposes. We will investigate both host kairomones (20, 21) and oviposition attractants (22–26) in different trap formats. We will test putative attractants by using laboratory-based behavioral bioassays to evaluate and shortlist candidate compounds for subsequent field evaluation of efficacy and persistence in both adult and ovitraps.

Deliverables for research area 1

1. Develop a comprehensive, early warning, laboratory-based sentinel disease surveillance system and determine the most useful and cost-effective predictive factors for epidemic dengue;
2. Develop predictive models in particular signature forecasting and a flagging system;
3. Study how viral evolution influences the virulence and epidemic potential of dengue viruses;
4. Develop and validate novel diagnostic assays for point-of-care use;
5. Develop improved field devices and attractants for vector monitoring;
6. Develop novel assays for virus detection and characterization in *Aedes* mosquitoes;
7. Study entomological and environmental indicators that may influence dengue transmission dynamics;
8. Develop geospatial modeling and risk maps;
9. Evaluate the predictive capability of climate variables (weather variability) and their operational utility for surveillance;
10. Relate the costs of dengue surveillance and prevention to their effect on the burden of the disease;
11. Engage policy makers on the sustainability of an integrated surveillance system.

Research area 2

Main research objective

Develop novel strategies to prevent dengue in children.

Rationale

In the absence of specific antiviral therapy and vaccination, other prevention strategies need to be developed. Vector control in itself has had poor results to date. Insecticide-treated fabrics have emerged as a key component of arboviral disease control efforts. Insecticide-treated bed nets (ITNs) have been shown to be a successful intervention for the control of malaria (27). The efficacy of ITNs in reducing malaria transmission is related to the night biting activities of anopheline mosquitoes, but their use may have little or no impact on dengue incidence because *Aedes* species have daytime feeding patterns. However, window curtains and domestic water container covers treated with insecticide can reduce densities of dengue vectors and potentially affect dengue transmission (28).

Additional novel approaches using insecticide-treated materials need to be evaluated for the control of dengue. Personal clothing would potentially be an excellent target because clothes are worn during day times. There have been a number of programs that have applied insecticides to personal clothing, but this has been limited to military and recreational markets.

There is an urgent need for integrated and complementary population-based strategies to protect vulnerable children. Children carry the main burden of morbidity and mortality caused by dengue (3, 29). Dengue is often more severe in children, and children have a higher risk for developing DHF (3, 30). Infection in children causes large disruptions in schooling and parental wage earning that in turn has direct impacts on nutrition and overall family health (31). For example, in Northern Thailand, it has been estimated that dengue contributes 465.3 DALYs per million population per year among school-aged children, which accounts for 15% of all DALYs loss from febrile illness in this age group (32). Over the past 40 years, 65% of reported cases in Thailand were confined to the 5–14 years age group. Because children of this age group spend a considerable amount of their day at school, it is likely that schools are primary sites for exposure to the daytime biting *Aedes* mosquitoes. Schools should therefore be a key target for control. From a pragmatic point of view, schools would be an easier target in comparison to dispersed populations. School uniforms are a cultural norm in most developing countries and are worn throughout the day on an almost daily basis. We hypothesize that impregnated school uniforms may reduce the incidence of dengue in school-aged children (33). To test our hypothesis, we will conduct a community-based randomized controlled trial of the efficacy of impregnated school uniforms on the incidence of dengue in school-aged children. Furthermore, we will test the repellency effect of school uniforms in different sizes and forms and with different impregnation methods in a laboratory setting.

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Deliverables for research area 2

1. Determine the efficacy of impregnated school uniforms in reducing the incidence of dengue in school-aged children;
2. Determine the protection efficacy of school uniforms impregnated with repellent under different laboratory scenarios;
3. Develop a cost-effectiveness framework and undertake an economic evaluation of the school-based preventive intervention;
4. Produce policy briefs and engage with policy makers to ensure the scalability of such school-based intervention programs, should the trial show efficacy.

Research area 3

Main research objective

Contribute to the understanding and predicting the risk of spread of dengue, in particular the risk of introduction and establishment in Europe, within the context vector competence, human mobility, and climate change.

Rationale

Dengue is the second most common cause of fever in returning international travellers, and the frequency of importation of dengue into currently non-endemic areas via travellers is increasing (34). There have been small outbreaks of dengue in Texas, USA, since 1980, all associated with increased transmission and importation from Mexico. In 2001, a small outbreak transmitted by *A. albopictus*, the first in 56 years, occurred in Hawaii. In 2009 and 2010, small outbreaks transmitted by *A. aegypti* occurred in Key West, Florida. Also, in 2010, the first authochthonous transmission of dengue occurred in Europe since before World War II: two cases in France and one in Croatia (*www.eurosurveillance.org*). *A. albopictus* is the only vector present in Europe with a wide and increasing distribution in many countries.

It is important to determine the risk of dengue becoming endemic in Europe. *A. albopictus*, although typically not an effective epidemic vector of dengue (9), is capable of transmitting dengue, and it is further spreading northward from countries bordering the Mediterranean. The risk of infection depends on vectorial capacity and viral replication rate in a temperate climate. The key question, therefore, is whether the presence of this vector is conducive to epidemic transmission in the event of importations into Europe.

Deliverables for research area 3

1. Monitor dengue importation into Europe;
2. Produce phylogenetic trees of imported dengue viruses to Europe using Bayesian modeling;
3. Compare the clinical manifestations and usefulness of the 2009 WHO dengue classification schemes in travellers (non-endemic populations) versus endemic populations (Sri Lanka);
4. Describe the breeding sites for *A. albopictus* in Southern France;
5. Determine the vectorial capacity of *A. albopictus* in a temperate climate;
6. Assess the impact of ultralow volume (ULV) spacing spraying on populations of adult *A. albopictus* in southern France;
7. Develop predictive models that integrate vector competence, vectorial capacity, and force of infection with global human mobility to assess the risk of epidemic transmission following the introduction of dengue viruses;
8. Produce interactive web-based tools on the risk of global spread of dengue, particularly to Europe.

Conclusions

Dengue fever is within the scope of the global health priorities. DengueTools is designed to address this priority. This cooperative and multidisciplinary project is also designed to improve the potential for new knowledge generation by integrating research groups with different scientific backgrounds, research centers from different European countries, and fostering research links between the North and South.

Effective surveillance and control for dengue is lacking. We will coordinate and facilitate one of the largest prospective integrated surveillance programs ever done in an endemic setting, in an attempt to find an answer to the most feasible strategy that will reliably predict new outbreaks and provide time-sensitive information for containment. Furthermore, we will attempt to develop novel inexpensive diagnostic tools, both for human diagnostics as well as for vector monitoring that will enhance an integrated surveillance system. Given the limited resources in many dengue endemic countries, it is of utmost importance to relate the costs of novel strategies for dengue surveillance and prevention to their effect on the burden of the disease. We will evaluate the economic value and benefit of each component of the integrated surveillance.

A second research area will focus on innovative strategies to reduce dengue infections in children by targeting schools. Reducing the incidence of dengue in school children will not only reduce morbidity and mortality but also reduce the number of school days lost, increase school performance, and reduce the economic burden on parents.

Dengue carries the risk of further geographic expansion and introduction into uninfected areas, including Europe. We will assess the risk of introduction of dengue under different future scenarios (such as climate change

and/or increased global mobility over the next decades) into Europe and develop predictive models to enhance Europe's preparedness for future dengue epidemics.

During the course of these 4 years, we will evaluate several novel tools and strategies that will have the potential to be scaled-up and, therefore, would need translation into public policy. Our consortium includes a health economist and policy analyst who will translate our research findings into evidence-informed policy making. Engagement with stakeholders and policy makers will start early in the project to ensure the potential for scaling up our recommendations.

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Conflict of interest and funding

A Wilder-Smith was the Principal Investigator of a Sanofi Pasteur funded Phase 2b vaccine trial for dengue. She has received speaker fees from GSK, Sanofi Pasteur and Novartis. Luke Alphey has employment and equity interest in Oxitec, Ltd. Oxitec is developing novel methods for the control of pest insects including *Aedes aegypti* and owns intellectual property relevant to the subject matter of this paper. Duane Gubler is on the scientific advisory boards of NITD, Inviragen, DVI, and ADITEC. He has received consultant fees from NITD and royalties and stock options from Inviragen. David Brooks works for TwistDx, a company that develops diagnostic assays. All other authors have no conflict of interest.

References

1. Gubler DJ. The global emergence/resurgence of arboviral diseases as public health problems. Arch Med Res 2002; 33: 330–42.
2. Beatty ME, Letson GW, Margolis HS. Estimating the global burden of dengue. In: Abstract Book: Dengue 2008. The Second International Conference on Dengue and Dengue Haemorrhagic Fever, Phuket, Thailand.
3. WHO. Dengue: guidelines for diagnosis, treatment, prevention and control. Geneva: World Health Organization; 2009.
4. Gubler DJ. Dengue, urbanization and globalization: the unholy trinity of the 21st century. Trop Med Health 2011; 39: 1–9.
5. Baggett HC, Graham S, Kozarsky PE, Gallagher N, Blumensaadt S, Bateman J, et al. Pretravel health preparation among US residents traveling to India to VFRs: importance of ethnicity in defining VFRs. J Travel Med 2009; 16: 112–8.
6. Beatty ME, Beutels P, Meltzer MI, Shepard DS, Hombach J, Hutubessy R, et al. Health economics of dengue: a systematic literature review and expert panel's assessment. Am J Trop Med Hyg 2011; 84: 473–88.
7. Wilder-Smith A, Gubler DJ. Geographic expansion of dengue: the impact of international travel. Med Clin North Am 2008; 92: 1377–90.
8. Wilder-Smith A, Ooi EE, Vasudevan SG, Gubler DJ. Update on dengue: epidemiology, virus evolution, antiviral drugs, and vaccine development. Curr Infect Dis Rep 2010; 12: 157–64.
9. Lambrechts L, Scott TW, Gubler DJ. Consequences of the expanding global distribution of *Aedes albopictus* for dengue virus transmission PLoS Negl Trop Dis. 2010;4:e656. Review.
10. Reiter P. Yellow fever and dengue: a threat to Europe? Euro Surveill 2010; 15: 19509.
11. Gubler DJ. Prevention and control of *Aedes aegypti*-borne diseases: lesson learned from past successes and failures. AsPac J Mol Biol Biotechnol 2011; 19: 111–4.
12. Focks DA, Daniels E, Haile DG, Keesling JE. A simulation model of the epidemiology of urban dengue fever: literature analysis, model development, preliminary validation, and samples of simulation results. Am J Trop Med Hyg 1995; 53: 489–506.
13. Leitmeyer KC, Vaughn DW, Watts DM, Salas R, Villalobos I, de C, et al. Dengue virus structural differences that correlate with pathogenesis. J Virol 1999; 73: 4738–47.
14. Runge-Ranzinger S, Horstick O, Marx M, Kroeger A. What does dengue disease surveillance contribute to predicting and detecting outbreaks and describing trends? Trop Med Int Health 2008; 13: 1022–41.
15. De Simone TS, Nogueira RM, Araujo ES, Guimaraes FR, Santos FB, Schatzmayr HG, et al. Dengue virus surveillance: the co-circulation of DENV-1, DENV-2 and DENV-3 in the State of Rio de Janeiro, Brazil. Trans R Soc Trop Med Hyg 2004; 98: 553–62.
16. Rico-Hesse R. Microevolution and virulence of dengue viruses. Adv Virus Res 2003; 59: 315–41.
17. Rosen L. The Emperor's New Clothes revisited, or reflections on the pathogenesis of dengue hemorrhagic fever. Am J Trop Med Hyg 1977; 26: 337–43.
18. Gubler DJ, Suharyono W, Lubis I, Eram S, Gunarso S. Epidemic dengue 3 in central Java, associated with low viremia in man. Am J Trop Med Hyg 1981; 30: 1094–9.
19. Holmes EC, Twiddy SS. The origin, emergence and evolutionary genetics of dengue virus. Infect Genet Evol 2003; 3: 19–28.
20. Knols BGJ, van Loon JJA, Cork A, Robinson RD, Adam W, Meijerink J, et al. Behavioural and electrophysiological responses of the female malaria mosquito *Anopheles gambiae* (Diptera: Culicidae) to Limburger cheese volatiles. Bull Entomol Res 1997; 87: 151–9.
21. Okumu FO, Killeen GF, Ogoma S, Biswaro L, Smallegange RC, Mbeyela E, et al. Development and field evaluation of a synthetic mosquito lure that is more attractive than humans. PLoS One 2010; 5: e8951.
22. Reiter P. A portable, battery-powered trap for collecting gravid Culex mosquitoes. Mosq News 1983; 4: 496–8.
23. Jackson BT, Paulson SL, Youngman RR, Scheffel SL, Hawkins B. Oviposition preferences of *Culex restuans* and *Culex pipiens* (Diptera: Culicidae) for selected infusions in oviposition traps and gravid traps. J Am Mosq Control Assoc 2005; 21: 360–5.
24. Sant'ana AL, Roque RA, Eiras AE. Characteristics of grass infusions as oviposition attractants to Aedes (Stegomyia) (Diptera: Culicidae). J Med Entomol 2006; 43: 214–20.
25. Ganesan K, Mendki MJ, Suryanarayana MVS, Prakash S, Malhotra RC. Studies of *Aedes aegypti* (Diptera: Culicidae) ovipositional responses to newly identified semiochemicals from conspecific eggs. Aust J Entomol 2006; 45: 75–80.
26. Sharma K, Seenivasagan T, Rao A, Ganesan K, Agarwal O, Malhotra R, et al. Oviposition responses of *Aedes aegypti* and *Aedes albopictus* to certain fatty acid esters. Parasitol Res 2008; 103: 1065–73.

Citation: Glob Health Action 2012, **5**: 17273 - DOI: 10.3402/gha.v5i0.17273

27. Muller O, Traore C, Kouyate B, Ye Y, Frey C, Coulibaly B, et al. Effects of insecticide-treated bednets during early infancy in an African area of intense malaria transmission: a randomized controlled trial. Bull World Health Organ 2006; 84: 120–6.
28. Kroeger A, Lenhart A, Ochoa M, Villegas E, Levy M, Alexander N, et al. Effective control of dengue vectors with curtains and water container covers treated with insecticide in Mexico and Venezuela: cluster randomised trials. BMJ 2006; 332: 1247–52.
29. Guzman MG, Kouri G. Dengue: an update. Lancet Infect Dis 2002; 2: 33–42.
30. Hammond SN, Balmaseda A, Perez L, Tellez Y, Saborio SI, Mercado JC, et al. Differences in dengue severity in infants, children, and adults in a 3-year hospital-based study in Nicaragua. Am J Trop Med Hyg 2005; 73: 1063–70.
31. Clark DV, Mammen MP Jr, Nisalak A, Puthimethee V, Endy TP. Economic impact of dengue fever/dengue hemorrhagic fever in Thailand at the family and population levels. Am J Trop Med Hyg 2005; 72: 786–91.
32. Anderson KB, Chunsuttiwat S, Nisalak A, Mammen MP, Libraty DH, Rothman AL, et al. Burden of symptomatic dengue infection in children at primary schools in Thailand: a prospective study. Lancet 2007; 369: 1452–9.
33. Wilder-Smith A, Lover A, Kittayapong P, Burnham G. Hypothesis: impregnated school uniforms reduce the incidence of dengue infections in school children. Med Hypotheses 2011; 76: 861–2.
34. Wilder-Smith A, Schwartz E. Dengue in travelers. N Engl J Med 2005; 353: 924–32.

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