



ENIVD Collaborative Laboratory Response Network ENIVD-CLRN



Proposal for a joint prospective study on imported Dengue and Chikungunya infections in Europe

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SURVEILLANCE POR EMERGING TROPICAL AND INFECTIOUS DISEASES (TROPNETEUROP)

Verona, 7 September 2009



ECDC ENIVD-CLRN - Windows Internet Explorer

http://www.enivd.de/ECDC/its_ecdc.htm

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The Project

The Task

The Steering Committee

The Partners

Secretariat

Contacts @ ECDC

WP 1 - Secretariat

WP 2 - Epidemic Intelligence

WP 3 - Outbreak Assistance

WP 4 - Preparedness

WP 5 - Training Activities

ENIVD


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Project of the ENIVD in co-operation with and funded by the ECDC


Establishment of a Collaborative Network of European Laboratories for Outbreak Assistance and Support co-ordinated by the European Network for Diagnostics of 'Imported' Viral Diseases (ENIVD)

The ENIVD Collaborative Laboratory Response Network (ENIVD-CLRN)





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The Task of the ENIVD-CLRN Project

- Background**

The threat posed by emerging and re-emerging communicable diseases and, further, by the intentional release of infectious agents in a susceptible population, has been receiving considerable attention at the national and international levels. Changes in lifestyle, travel, and migration, as well as other factors such as climate change and terrorism have increased the vulnerability of the human population to imported, rare, and emerging infections. Numerous virus outbreaks serve as reminders that severe infections can be imported into Europe by travellers coming from regions with a high incidence, and then spread quickly.

Tackling health threats requiring an early recognition, diagnostic, and a rapid response has resulted in much closer co-operation among the member states and the central institutions of the borderless European Union (EU), where every day millions of people move about freely and goods of all sorts are speedily transported at great distances.

Never before has the need for closer co-operation between international organisations, such as the World Health Organization (WHO) or the European Centre for Disease Prevention and Control (ECDC), and entities such as the EU and individual countries, become so apparent and so acknowledged.

While the majority of the EU member states have a good capacity for most of the common communicable disease agents, certain key issues could be identified in the previous ENIVD CAP/QA study ("Diagnostic capacity for emerging and re-emerging viral diseases") that need to be addressed to improve the diagnostic capacity and increase the European preparedness to outbreak-prone diseases, imported agents, rare agents, unknown agents, or outbreaks related to intentional release.

Currently, there are several rare and imported, emerging and re-emerging outbreak-prone infectious diseases [see below] not covered by the European Disease Specific Programme and its network (based on decision no. 2119/98/EC), because the funding for the respective Dedicated Surveillance Networks (DSNs) in this programme ran out.

Thus, the ECDC seeks to establish a collaborative network of European experts/laboratories for outbreak detection, identification and diagnostic support to those kinds of viral agents.


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Steering Committee of the ENIVD-CLRN Project

Updated: 22 November 2008

 <p>Prof. Matthias Niedrig Robert Koch-Institut, Berlin matthias.niedrig@rki.de Responsible for project administration, co-ordination and Workpackage 1</p>	 <p>Dr. Oliver Donoso Mantke Robert Koch-Institut, Berlin donoso@rki.de Deputy, for project administration co-ordination and communication Responsible for Workpackage 4</p>	 <p>Dr. Antonio Tenorio Centro Nacional de Microbiología, Instituto de Salud Carlos III, Madrid atenorio@isciii.es Responsible for Workpackage 2</p>
 <p>Dr. Jean-Claude Manuguerra Institut Pasteur, Paris jmanuguerra@pasteur.fr Responsible for Workpackage 3</p>	 <p>Dr. Graham Lloyd Health protection Agency, Porton Down graham.lloyd@hpa.org.uk Responsible for Workpackage 5</p>	

The Task of Work Package 2 Epidemic Intelligence activities

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● Objectives

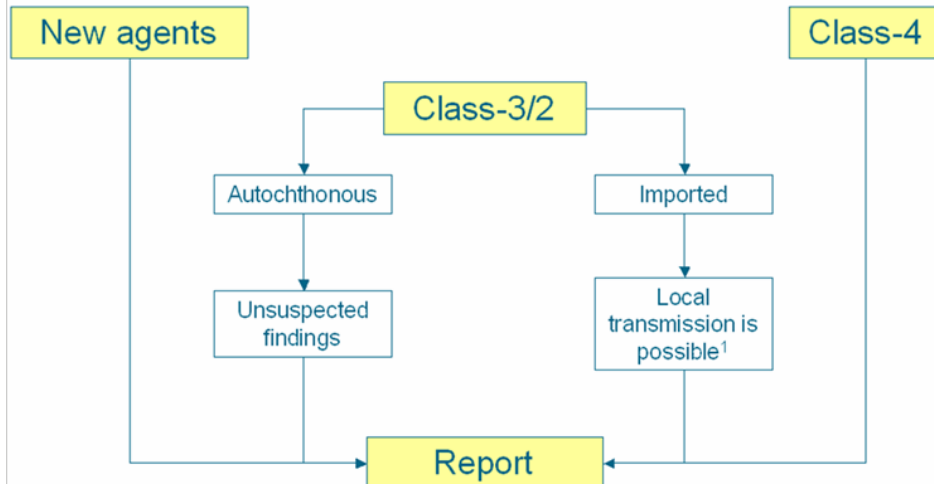
The main objectives of WP 2 consist in the active participation of the ENIVD-CLRN in the epidemic intelligence activities of the ECDC (support outbreak and cluster detection, verification and investigation) for the entire duration of the tender, and in advice and guidance for risk assessment and risk communication from the microbiologist's perspective. For this purpose the ENIVD-CLRN will maintain a 24/7 on call duty system with a multi-disciplinary panel of laboratory experts (by a generic dial-in number and e-mail address) through which the ECDC can access the expertise within the Network at anytime.

To achieve the objectives mentioned above WP 2 is structured into four sub-tasks:

● Subtask 1 - Preparation of a weekly "threat" report

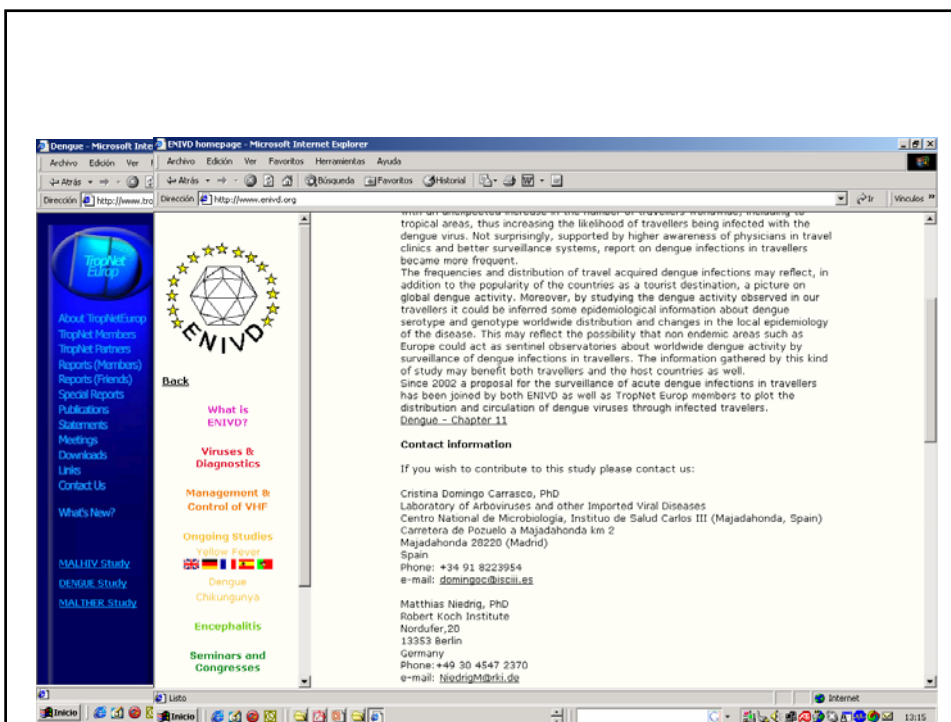
The ENIVD-CLRN will inform through dissemination by the Network secretariat ECDC and the participating Network members about (a) new suspected case(s)/clusters/outbreaks of disease covered by this tender detected through the Network. For this purpose weekly ENIVD-CLRN threat reports from the microbiologist's perspective will be issued on Thursday and circulated to the Network members and ECDC prior to the weekly epidemic intelligence meeting (see Sub-task WP 2.2). [Diagram](#)

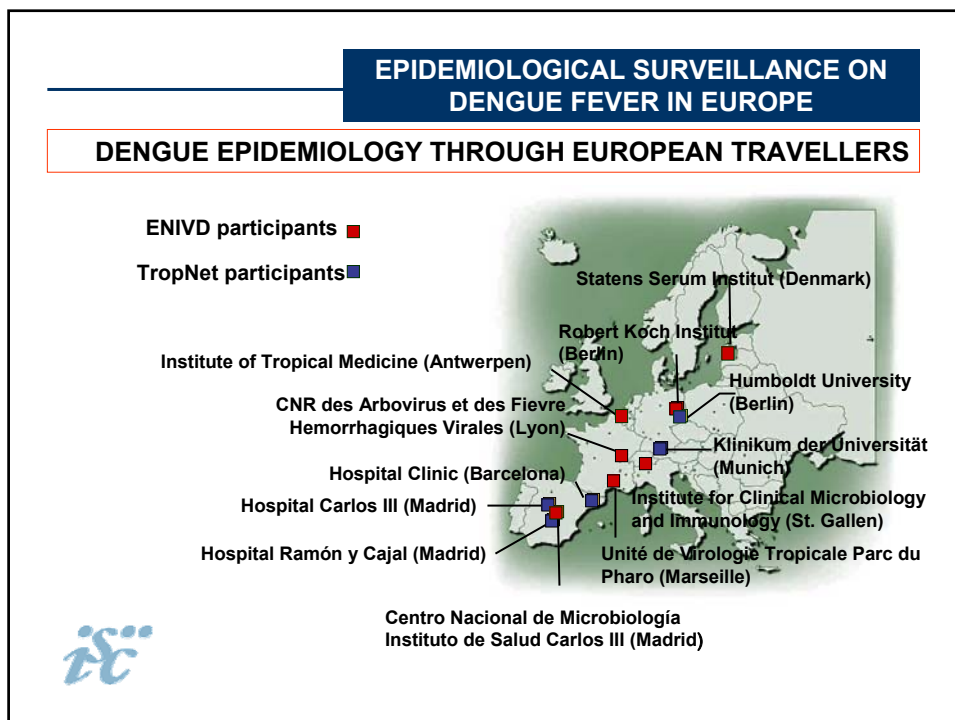
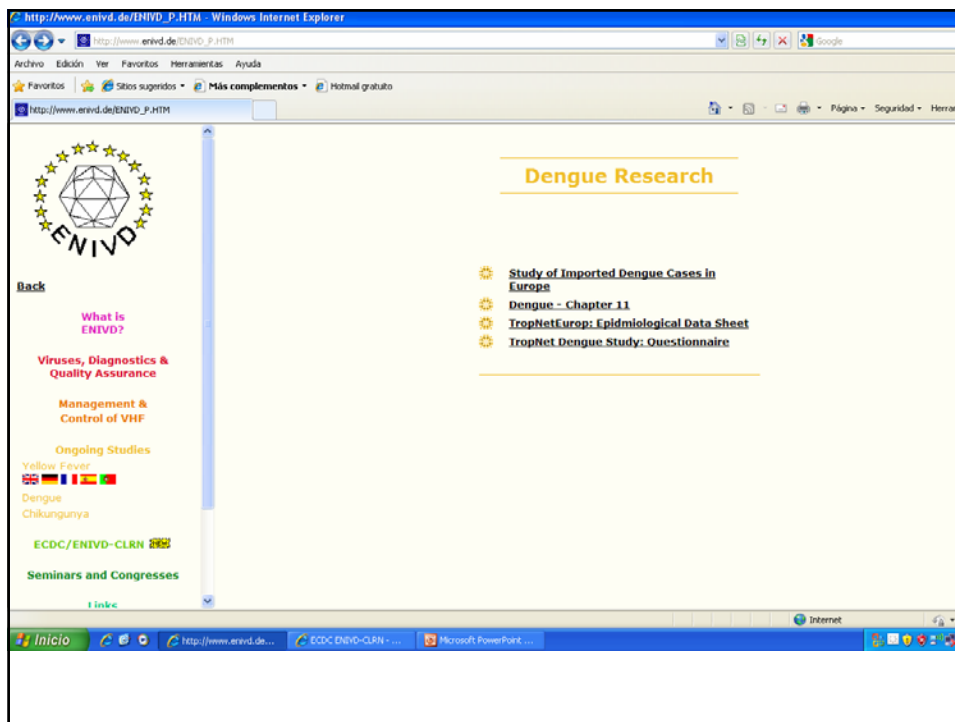
Algorithm for an informal weekly "threat" report at laboratory level



¹CHIKV, YFV, DENV in areas with presence of *Aedes albopictus* or *Ae. aegypti*; other similar scenarios

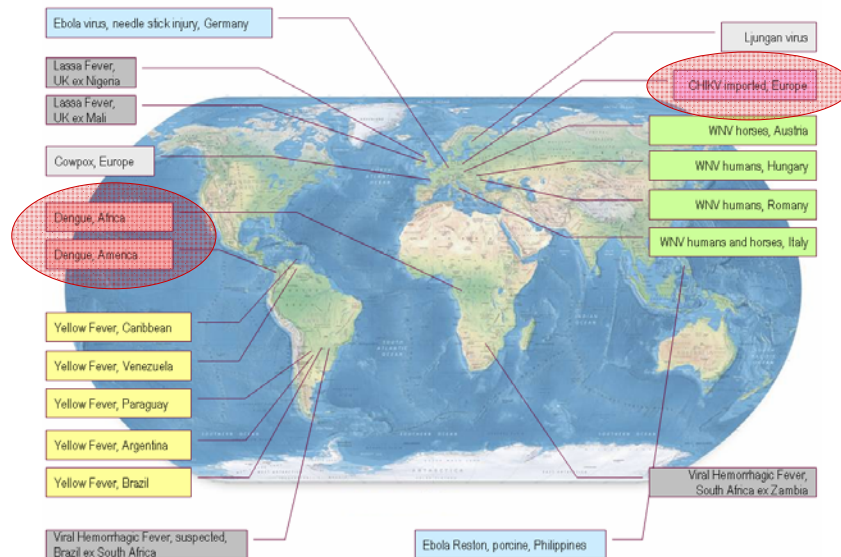
- **Subtask 2 - Participation in ECDC's weekly epidemic intelligence meeting**
 The ENIVD-CLRN will assure that appropriate representatives of the Network participate via telephone or videoconference in the epidemic intelligence "roundtable" meeting in which information on ongoing events is reviewed once a week, on Thursday, at 11:30 in preparation for the ECDC Communicable Disease Threat Report (CDTR). This virtual meeting should not exceed 30 minutes unless a threat requires specific attention (see Sub-task WP 2.3). The Network is expected to provide information about the microbiological aspects of threats caused by agents covered within this tender.
- **Subtask 3 - Ad hoc advice/guidance for risk assessment and risk communication**
 The ENIVD-CLRN will provide, on ad hoc basis, timely advice on questions regarding microbiological issues of diseases covered by this tender and assist in risk assessment (e.g. questions on the agent, agent properties, interpretation of different test formats and protocols, laboratory capacity within Europe, biosafety and biosecurity issues, methods for prevention and control).
 Especially for this purpose the ENIVD-CLRN will maintain a 24/7 on call duty system with a multidisciplinary panel of laboratory experts (by a generic dial-in number and e-mail address) - composed by ENIVD partners, representatives of outbreak assisting laboratories and external experts - through which the ECDC can access the expertise within the Network at anytime.
- **Subtask 4 - Participation in the Epidemic Intelligence System (EPIS)**
 The ENIVD-CLRN will actively participate in/contribute to the EPIS, a platform for technical risk assessment and risk communication that will be linked to the Early Warning and Response System (EWRS) IT application. It is foreseen that EPIS becomes a collaborative communication tool that facilitates the exchange of technical information on specific events between the member states. EPIS will have customisable and moderated portals per community (thematic forums, alert forums, event specific forums) and allow for the combination of 'event-based' and 'indicator-based' surveillance as input and for signals to the EWRS. Upon activation of the EPIS by ECDC, the Network is expected to animate a moderated forum for Network members to discuss issues arising from epidemic intelligence activities.







Weekly Epidemic Intelligence Meeting



Background: recent history

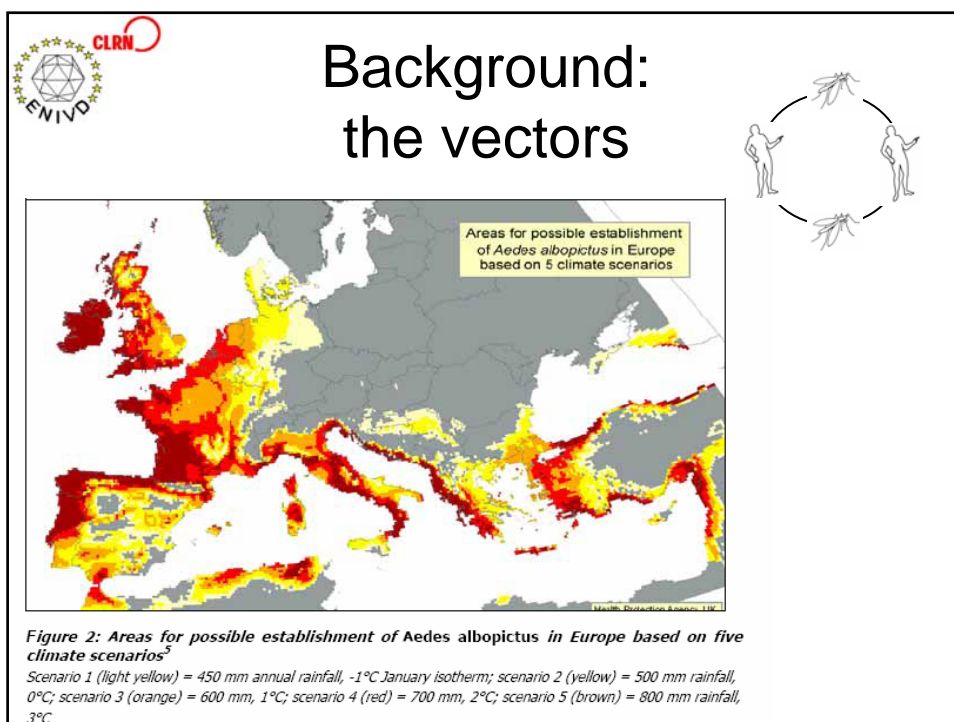
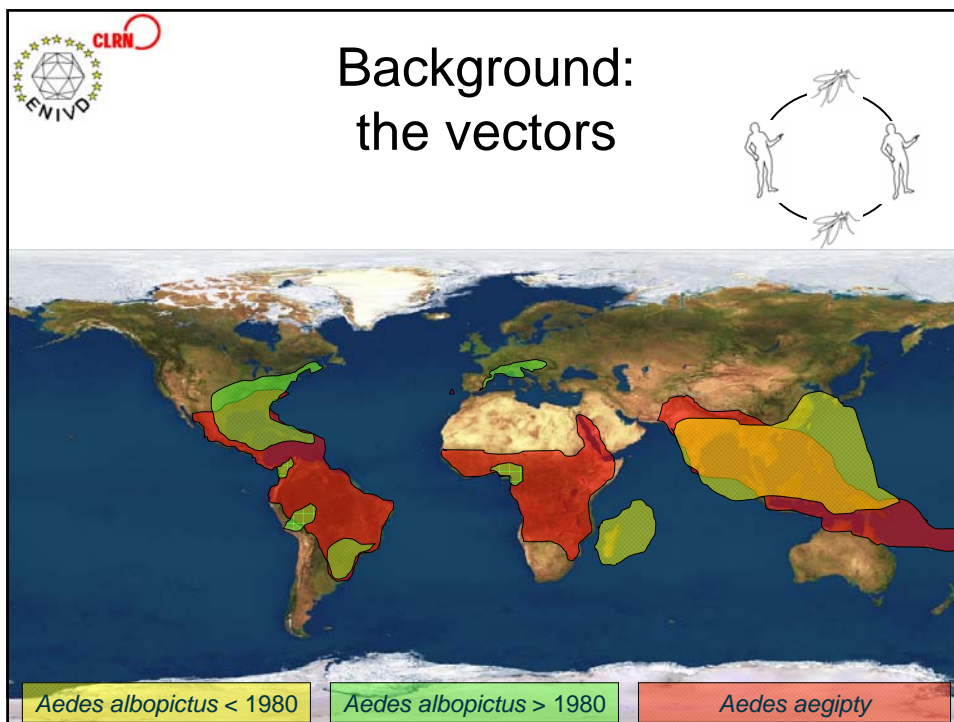
Eurosurveillance, Volume 12, Issue 36, 06 September 2007

Articles

Citation style for this article: Angelini R, Finarelli AC, Angelini P, Po C, Petropulacos K, Macini P, Fiorentini C, Fortuna C, Venturi G, Romi R, Majori G, Nicoletti L, Rezza G, Cassone A. An outbreak of chikungunya fever in the province of Ravenna, Italy. Euro Surveill. 2007;12(36):pii=3260. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=3260>

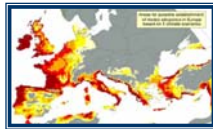
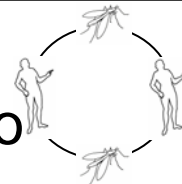
An outbreak of chikungunya fever in the province of Ravenna, Italy

R Angelini¹, AC Finarelli², P Angelini², C Po², K Petropulacos³, P Macini², C Fiorentini⁴, C Fortuna⁴, G Venturi⁴, R Romi⁴, G Majori⁴, L Nicoletti⁴, G Rezza⁴, A Cassone (cassone@iss.it)⁴

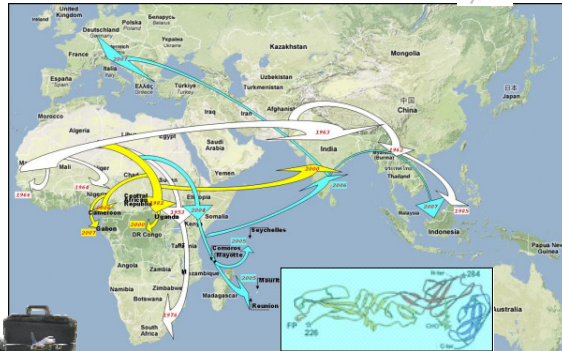




Background: an integrated scenario



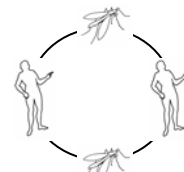
- The vectors
- The reservoirs
- The virus



Chikungunya virus adapts to tiger mosquito via evolutionary convergence: a sign of things to come?
Xavier de Lamballerie¹, Eric Leroy², Rémi N Charrel¹, Konstantin Tssetsarkin³, Stephen Higgs³ and Ernest A Gould¹



Background: the virus

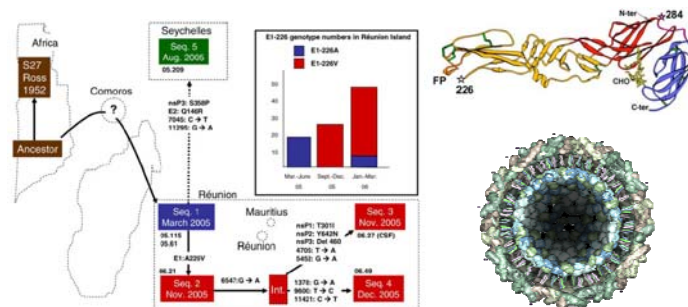


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PLOS MEDICINE

Genome Microevolution of Chikungunya Viruses Causing the Indian Ocean Outbreak

Isabelle Schuffenecker^{1*}, Isabelle Itman², Alain Michault³, Séverine Murri¹, Lionel Frangeul⁴, Marie-Christine Vaney^{5,6}, Rachel Lavenir², Nathalie Pardigon⁷, Jean-Marc Reynes⁸, François Pettinelli⁹, Leon Biscornet¹⁰, Laure Diancourt², Stéphanie Michel¹, Stéphane Duquerroy^{5,6,11}, Ghislaine Guigon², Marie-Pascale Frenkiel¹, Anne-Claire Bréhin⁷, Nadège Cubito³, Philippe Desprès⁷, Frank Kunst¹², Félix A. Rey^{2,13}, Hervé Zeller¹, Sylvain Brisse^{1*}

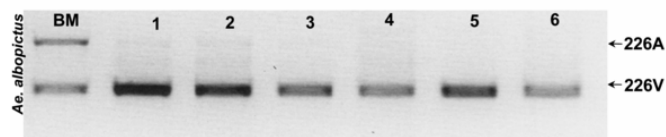




Background: the virus

A Single Mutation in Chikungunya Virus Affects Vector Specificity and Epidemic Potential

Konstantin A. Tsetsarkin, Dana L. Vanlandingham, Charles E.
McGee, Stephen Higgs*

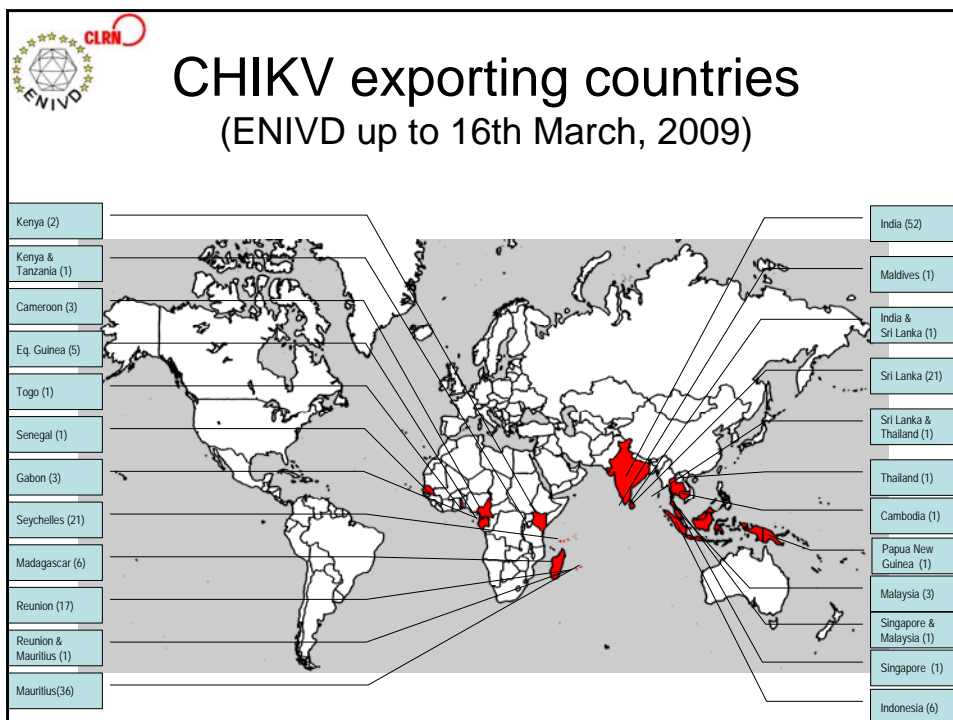
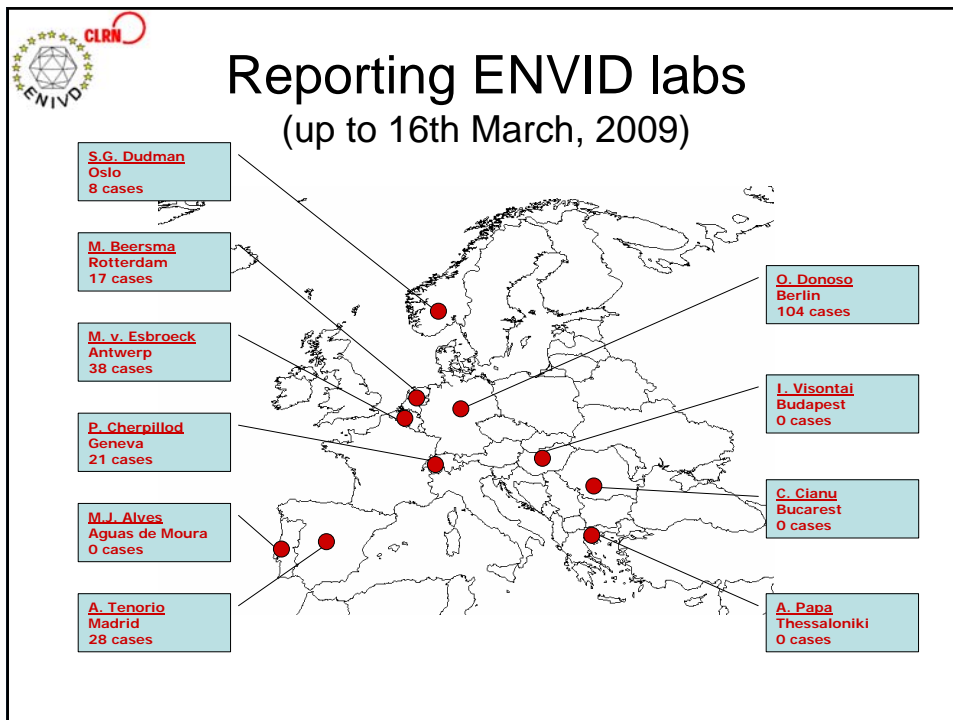


Effect of E1-A226V Mutation on CHIKV Transmission by *Ae. albopictus* :



Retrospective study on CHIKV imported infections in Europe

- To identify those countries exporting CHIKV after 2005
- To disseminate this information
 - Public Health
 - Virologists
 - Clinicians





Reported CHIKV activity (ProMed 9th March, 2009)



ENIVD reported CHIKV infections (up to 16th March, 2009)

ENIVD + ProMed ENIVD only





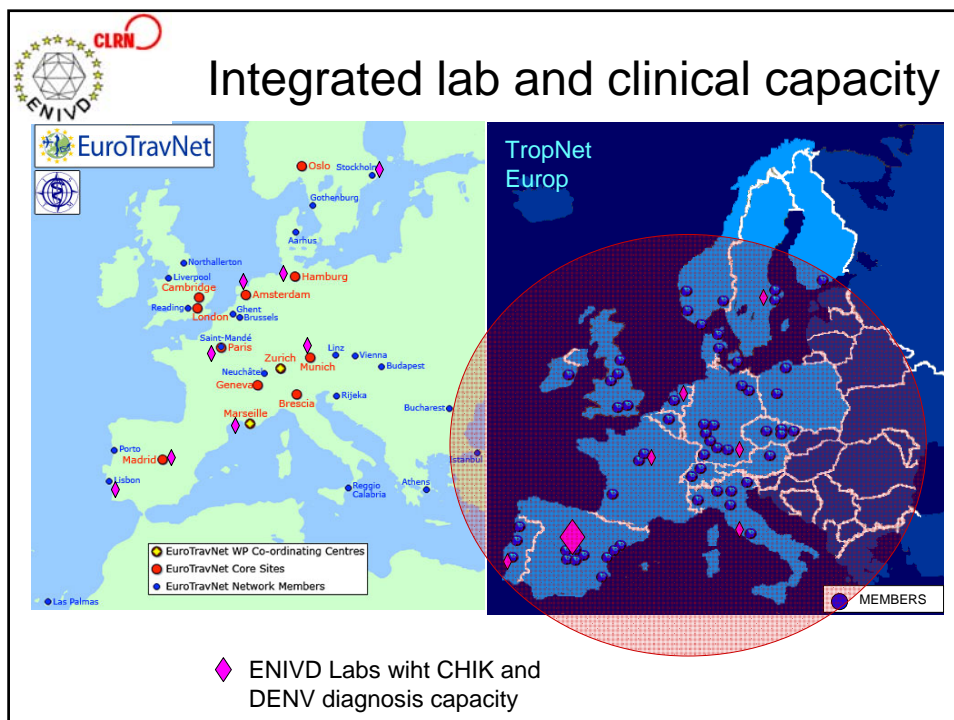
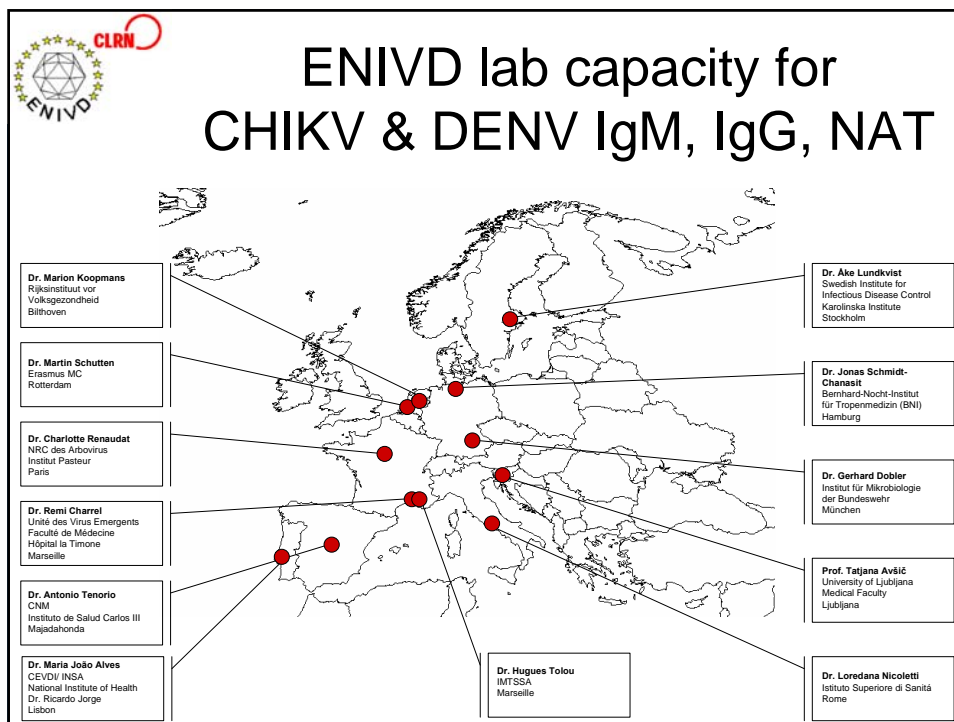
To conclude

- The ENIVD collaborative study
 - Detected imported infections from all of the countries reported at ProMed
 - Five CHIKV exporting countries not previously reported by ProMed have been identified with the ENIVD reports up to 16-March-2009:
 - Kenya
 - Togo
 - Gabon
 - Cambodia
 - Papua New Guinea
- A prospective, collaborative study will allow:
 - To compare clinical symptoms, signs and analytical data for imported Chikungunya and Dengue in Europe
 - To obtain a map of CHIKV & DENV imported cases
 - To trace the global distribution of viral genotypes for CHIKV and DENV



The proposal Prospective study

- **Imported chikungunya and dengue infections in European travellers**
 - Prospective study (Proposed dates: March 2010 – December 2012)
 - Reporting networks
 - ENIVD capacitated labs
 - Labs with IgM, IgG and PCR for CHIKV & DENV
 - TropNetEurop and/or EuroTravNet
 - Clinical units linked or not to ENIVD capacitated labs



[illegible]

- Virological markers on acute samples (first week after fever):
 - IgM results
 - IgG results
 - PCR results
 - If PCR or cell culture positive results:
 - Serotype (for DENV), and genotype (both for DENV and CHIKV)
 - E226 sequence for CHIKV



A New Tool for the Diagnosis and Molecular Surveillance of Dengue Infections in Clinical Samples

C. Domingo^{*,#}, G. Palacios^{**,}, M. Niedrig^{***}, M. Gabrerizo^{*}, O. Jabado^{**,},
N. Reyes^{*}, W.I. Lipkin^{**} and A. Tenorio^{*}

Table. Primers used in RT-nested PCR assays and sequencing

Primer ^a	Sequence ^b	Genome position [†]	PCR
S1871DEN1	5'-TGGCTGAGACCCARCATGGNAC-3'	1869 to 1890	RT-PCR
S1871DEN2	5'-TAGCAGAAACACARCATGGNAC-3'	1871 to 1889	
S1871DEN3	5'-TCTCCGAAACGCARCATGGNAC-3'	1863 to 1884	
S1871DEN4	5'-TGGCAGAAACACARCATGGNAC-3'	1873 to 1894	
AS2622DEN1	5'-CAATTCATTGATATTGTTCCAC-3'	2620 to 2644	RT-PCR
AS2622DEN2	5'-CAATTCGTTGTTATTGTTCCAC-3'	2622 to 2646	
AS2622DEN3	5'-CAGTTCATTGCTATTGTTCCAC-3'	2614 to 2638	
AS2622DEN4	5'-TAGCTCGTTGTTATTGTTCCAC-3'	2624 to 2648	
S2176DEN1	5'-ATCCTGGGAGACACGNTGGG-3'	2174 to 2195	Nested
S2176DEN2	5'-ATTTTGGGTGACACAGCNTGGG-3'	2176 to 2197	
S2176DEN3	5'-ATCCTGGGAGACACGNTGGG-3'	2168 to 2189	
S2176DEN4	5'-ATTCTAGGTAAACAGCNTGGG-3'	2178 to 2199	
AS2504DEN	5'-TGRAAYTTRTAYTGTCTGCC-3'	2506 to 2527 DEN-1 2504 to 2525 DEN-2 2496 to 2517 DEN-3 2506 to 2527 DEN-4	Nested

^aPrimers names beginning with "S" indicate a genome (plus)-sense orientation; names beginning with "AS" indicate a complementary sense orientation.

[†]The genome positions are given according to each dengue virus serotype prototype strain (DEN-1; strain Mochizuki, DEN-2; strain Jamaica N-109, DEN-3; strain H87, DEN-4; strain 814669)

^bDegenerate positions: N:A/C/G/T, R:A/G, Y:T/C

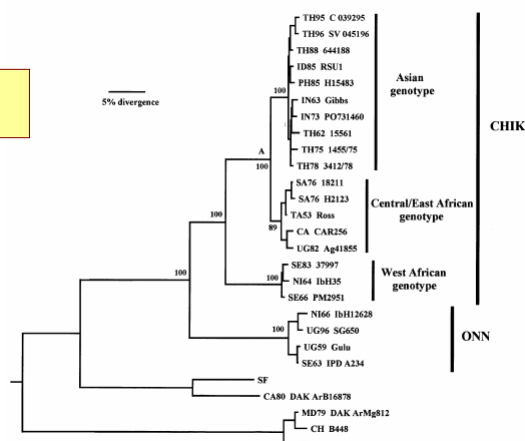


Re-emergence of chikungunya and o'nyong-nyong viruses: evidence for distinct geographical lineages and distant evolutionary relationships

Ann M. Powers, Aaron C. Brault, Robert B. Tesh and Scott C. Weaver

Department of Pathology and Center for Tropical Diseases, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-0609, USA

AF369024:10264-11307
Includes E226-CHIKV position





Costs

- Analytical studies (clinical partner)
- Virological markers (ENIVD partner)
- Other costs (ENIVD-CLRN WP2)
 - Tubes for the aliquots with AVL or other RNA stabilizing buffer?
 - If required, transport and assay of samples for confirmatory studies if required by the ENIVD labs
 - If required, sequencing of positive samples not previously characterized by the ENIVD labs



Communication tools

- Web accession to all the participants
- Hosted by all the Networks in the project





Expected papers

- Clinical and analytical markers associated to CHIKV and DENV imported infections in Europe.
 - Differential diagnosis.
 - Epidemiology
- World map of CHIKV genotypes and lineages
- World map of DENV serotypes, genotypes and lineages
- Others?



Next steps

- To propose the project to the three networks (May, 2009)
- To confirm the ENIVD capacitated laboratories (May, 2009)
- To identify pre-existing links between clinical and virology groups in Europe (May-June, 2009)
- To obtain a preliminary compromise of the pairs of partners (June-July, 2009)
- To define the scientific coordinator of the project and Networks coordinators for the project (May-July, 2009)
 - To define the clinical coordinator (June-July, 2009)
 - To define the coordinator on virology (May-July, 2009)
- To write a project and obtain a consensus between the partners (September, 2009)
- To obtain the signed agreement on the project by the partners (October 2009)
- To obtain an operative on-line database for the project (December, 2009)
- To start the project (January, 2010)



Next steps

- To propose the project to the three networks (May, 2009)
- To confirm the ENIVD capacitated laboratories (May, 2009)
- To define the scientific coordinator of the project and Networks coordinators for the project (September, 2009)
 - To define the clinical coordinator (September, 2009)
 - To define the coordinator on virology (Antonio Tenorio)
- To identify pre-existing links between interested clinical and virology groups in Europe (September-October, 2009).
 - Send e-mail to the TropNet coordinator cc atenorio@isciii.es
- To write a project and obtain a consensus between the partners (November, 2009)
- To obtain the agreement on the project by the participant partners (December, 2009)
- To obtain an operative on-line database for the project (January-February, 2010)
- To start the project (March, 2010)