

How to design intranational deferral
Malaria in Greece

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Malaria - Key Facts

- Malaria is a life-threatening disease caused by parasites that are transmitted to humans through the bites of infected female *Anopheles* mosquitoes (*P. falciparum, vivax, malariae, ovale*)

- WHO estimates that 3.2 billion people live in areas at risk of malaria transmission in 106 countries and territories

- In 2015, out of 91 countries and areas with ongoing malaria transmission, Africa was home to 90% of malaria cases and 92% of malaria deaths (mostly among children)

WHO 2017

The most ancient genetic evidence of malaria



Tutankhamun 1341 -1323 BC 18$^{\eta}$ Dynasty

Transfusion Transmitted Malaria (TTM)

- TTM is sporadically reported in USA and Europe; focus on the risk of transmission in travelers to endemic areas and in permanent residents with origin from endemic areas
- In the USA, most cases could have been prevented if the implicated donors had been deferred according to established guidelines (CDC, 2017)
- France, UK and other countries not affected by malaria have in recent years changed their travel-related blood donor selection policy

- An outbreak of locally acquired *P. vivax* malaria in Greece (start in 2009, peak in 2011) raised the issue of how to define spatial boundaries of affected areas for blood donor deferral, in relation to blood safety and sustainability

  The fact that no laboratory test is sufficiently sensitive for reliable detection of low parasitaemia in asymptomatic potential blood donors who may have been infected, has also raised questions about blood screening strategies

The History of Malaria in Greece

Endemic until mid-20th century

- 1974: WHO declared Greece malaria-free following an intensive eradication programme (1946-1960)
- 1975 - 2008
  - 20 - 50 imported cases reported annually to the Hellenic CDC, the majority travel-related
  - Sporadic locally acquired cases without travel history: 1991, 1999, 2000

- 2009 -2016: epidemic

P. vivax re-emerged in pre-eradication malaria hotspots, both as sporadic introduced cases and as clusters, in persons without travel history to a malaria endemic country.

Public health and blood safety measures were implemented to avoid re-establishment of the disease

Malaria in Greece: Surveillance and Intervention

Office for Vector-borne Diseases
Department for Epidemiological Surveillance and intervention
Hellenic Centre for Disease Control & Prevention (HCDCP)

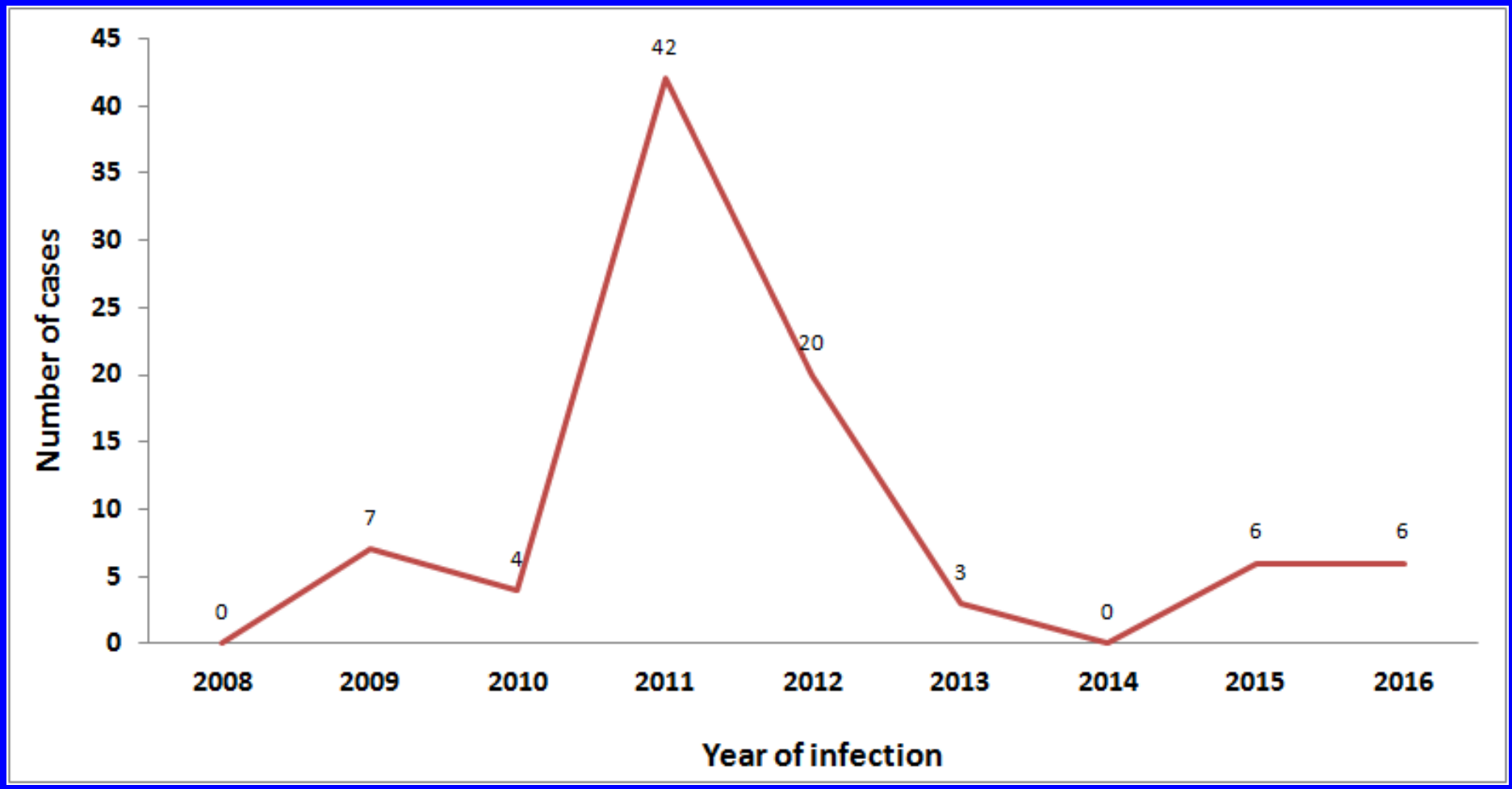
HCDCP
HELLENIC CENTER FOR DISEASE CONTROL & PREVENTION
MINISTRY OF HEALTH

Reported malaria cases by year of onset and case classification, Greece, 2009-2016

Year of onset of symptoms	Case classification		Total
	Imported cases	Locally acquired (*P. vivax*)	
2009	44	7	51
2010	40	4	44
2011	54	42	96
2012	73	20	93
2013	22	3	25
2014	38	0	38
2015	79	6	85
2016	111	6*	117
Total	**461 (84%)**	**90* (16%)**	**551 (100%)**

*Additionally: 2 cases of unknown classification
2 cases attributed to the 2015 transmission period

Locally acquired malaria cases by year of infection, Greece, 2009 – 2016



Classification of 54 malaria cases in the Evrotas hotspot

Year of symptoms onset	Locally acquired cases	
	Greece	Evrotas
2009	7	6
2010	4	1
2011	42	36
2012	20	10
2013	3	0
2014	0	0
2015	6	1
2016	8	0
Total	**90 (100%)**	**54 (60%)**



Action Plan
for the Management of Malaria, 2012 - 2017

- Risk assessment - Risk levels 0-3 (national experts consensus)

1. Enhanced passive malaria surveillance
2. Active laboratory diagnosis of malaria
3. Active case detection (focus investigation all over Greece, daily door–to-door proactive case detection in high risk areas e.g.Evrotas)
4. Case management (case classification, place of exposure, place of residence)
5. Entomological surveillance and control activities - Environment and vector investigation
6. Communication (health professionals, public, MoH, ECDC, WHO)
7. Blood safety and haemovigilance measures

Multisectoral WG for the designation of areas affected by Vector Borne Diseases
Committee for the Prevention and Management of Tropical Diseases – Ministry of Health

Active case detection, Evrotas, Lakonia





Active case detection, Evrotas, Lakonia



Contribution of genotyping of *P. vivax* malaria cases in Greece

- Reveals the specific alleles inherited by an individual
- Detects and characterizes genetic variability, aiming to identify:

  - the origin of a strain that caused an epidemic
  - the pattern of spread
  - relapses
  - current or previous infections

The main idea is: strains that share more identical markers (alleles), are more likely to share a more recent common ancestor

- For *P. vivax,* one of the most studied genes, merozoite surface protein-3α (Pvmsp-3α), highly polymorphic
- Microsatellite markers (MS) also applied in *P. vivax* genetic diversity studies, increasing analysis of results

NATIONAL SCHOOL OF PUBLIC HEALTH
ATHENS SCHOOL OF HYGIENE 1929-1994

Measures for blood safety against Malaria in Greece, 2009-2017

General precautionary measures

Malaria (*)	
— individuals who have lived in a malarial area within the first five years of life	**3** years following return from last visit to any endemic area, provided person remains symptom free; may be reduced to 4 months if an immunologic or molecular genomic test is negative at each donation
— individuals with a history of malaria	**3** years following cessation of treatment *and* absence of symptoms. Accept thereafter only if an immunologic or molecular genomic test is negative
— asymptomatic visitors to endemic areas	**6** months after leaving the endemic area unless an immunologic or molecular genomic test is negative
— individuals with a history of undiagnosed febrile illness during or within six months of a visit to an endemic area	**3** years following resolution of symptoms; may be reduced to 4 months if an immunologic or molecular test is negative

in conformity with Directive 2004/33/EC and
the Guide to the Preparation, Use and Quality Assurance of Blood Components-EDQM, Council of Europe, 16th edition

Measures for blood safety against Malaria in Greece, 2009-2017

Specific measures for affected areas with proven ongoing transmission of malaria (locally acquired)

- Suspension of blood sessions in the affected areas and surrounding agricultural villages within a radius of 10 km (2009-2012) , reduced to 6 km (2013-2017)

  This distance criterion is based on the dispersal range for Anopheles mosquitoes estimated to 1-3 km.

  This means that a malarial risk area should be a circle of 2-6 km radius around the reported transmissions, taking into account the geomorphology of the area

  Temporary deferral from blood donation of asymptomatic persons residing or working in the above areas and visitors (at least one overnight stay) for a period of 6 months

- In some areas blood screening for malarial antibodies of for malarial DNA

The smallest unit of an administrative territorial division (Nomenclature of Territorial Units for Statistics lever 3- NUTS3) that covers the malarial risk area should be assigned for the spatial targeting of blood safety measures for malaria (ECDC,2013)

Multisector Working Group on the definition of affected areas by vector borne diseases and the designation of affected areas for the implementation of blood safety measures

Haemovigilance measures

- **Post-donation information**

  Request all donors to inform blood collecting services in the event of symptoms relevant to malaria or fever of unknown origin within 15-30 days after donation, in order to examine for malaria

- **Post–transfusion information**

  In case of transfusion-transmitted malaria, apply look-back and traceability studies, including call up and blood testing of implicated blood donors

Maintaining the safety and the sustainability of the blood supply

Blood safety measures applied to affected areas are defined, assigned/un-assigned in a timely manner by the group of experts

Measures follow a risk assessment based on

- number of cases identified, plasmodia species present,
- spread of cases, time of the year when the local transmission occurs and affected population

The identification of the first case(s) triggered the initial planning of interventions

The measures continued along with active surveillance until the end of the mosquito season without new cases reported

Measures were recalled, however incubation and deferral periods should be taken into consideration in relation to season length, the malarial antibody screening of donated blood in order to continue or not at least until the start of the next malaria season (this whole period amounts to about 18 months)

The group of Experts used the data of Evrotas Lakonia, a hotspot of locally acquired malaria in 2011 and 2012 to validate the above approach

ECDC, Expert Opinions 2012-2013

Withdrawal of blood safety measures

De-characterization of affected areas or continuation of intense surveillance and prophylaxis in areas at risk for malaria in accordance with the ECDC Experts Opinion 2013 and the Consensus of National Experts

RESULTS I

Selective blood donation screening for evidence of malaria in affected areas , 2009-Jan.2015

Year	PCR	Immunological	Total	Results
2009	0	158	158	Negative
2010	0	106	106	Negative
2011	418	61	479	Negative
2012	513	140	653	Negative
2013*	279	-	279	Negative
2014 *	519	-	519	Negative
2015 *	61	-	61	Negative
Total	**1790**	**465**	**2255**	**Negative**

* In Lakonia only, for precautionary reasons

RESULTS II

Haemovigilance data 2009 – 30 April 2017

Post-donation and post-transfusion information throughout the entire outbreak have not detected any case of Transfusion Transmitted Malaria.

The absence of TTM cases suggests that measures applied to an area broader than malarial risk areas could prevent donations not only by exposed residents in the area but also by visitors and workers from the other parts of the municipality.

RESULTS III
The impact of temporary donor deferral on the blood supply

- Reduction 10% (range 2-24%) in blood collection in Attica, where 60% of total blood consumption takes place, particularly in the areas affected by Malaria and WNV;

- Postponement/delays of blood transfusions;

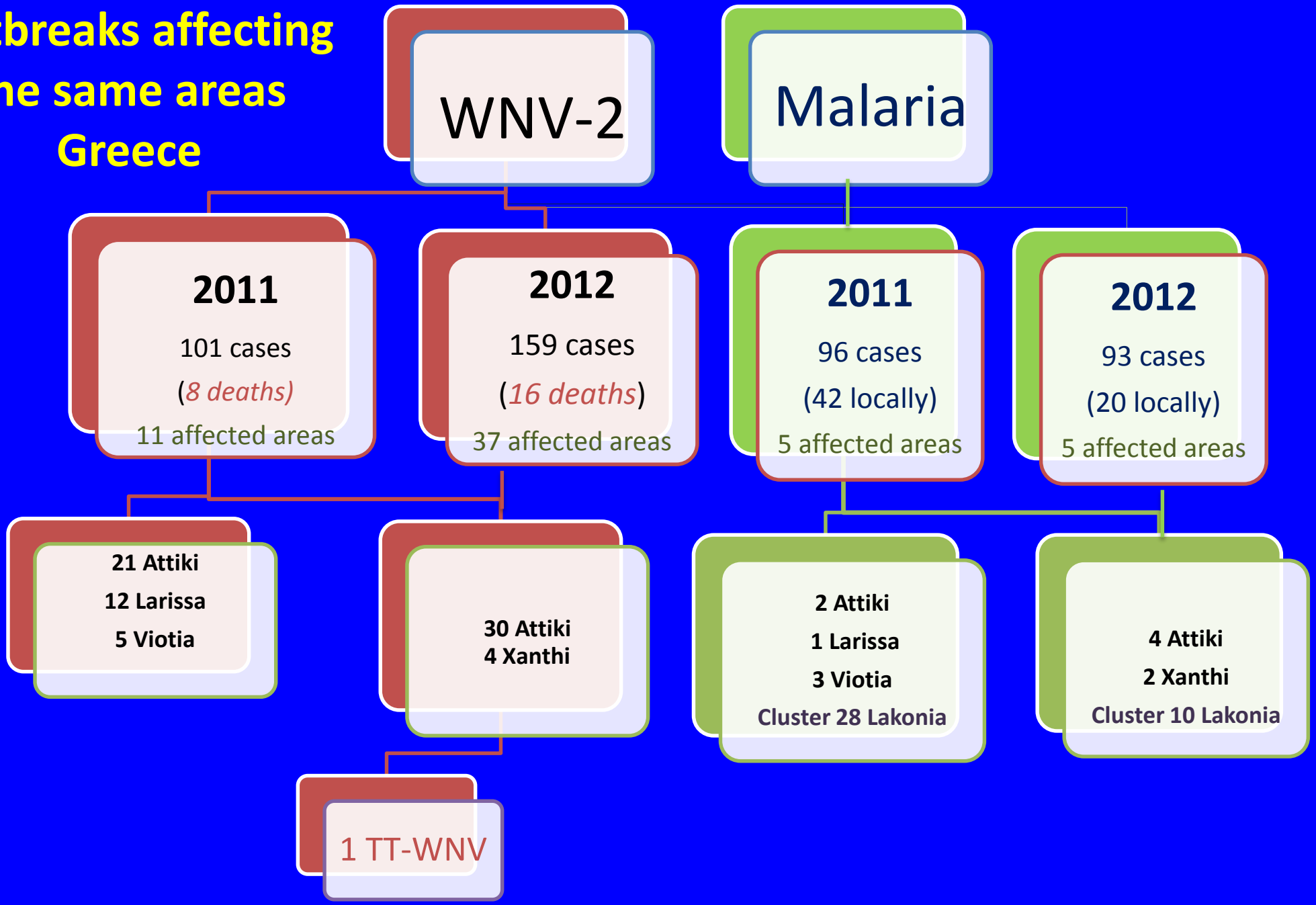
- Serious difficulties in the transfusion of platelets in oncological patients and in bone marrow transplantations;

- Hypotransfusion of the chronically transfused thalassaemic patients and emergency cases;

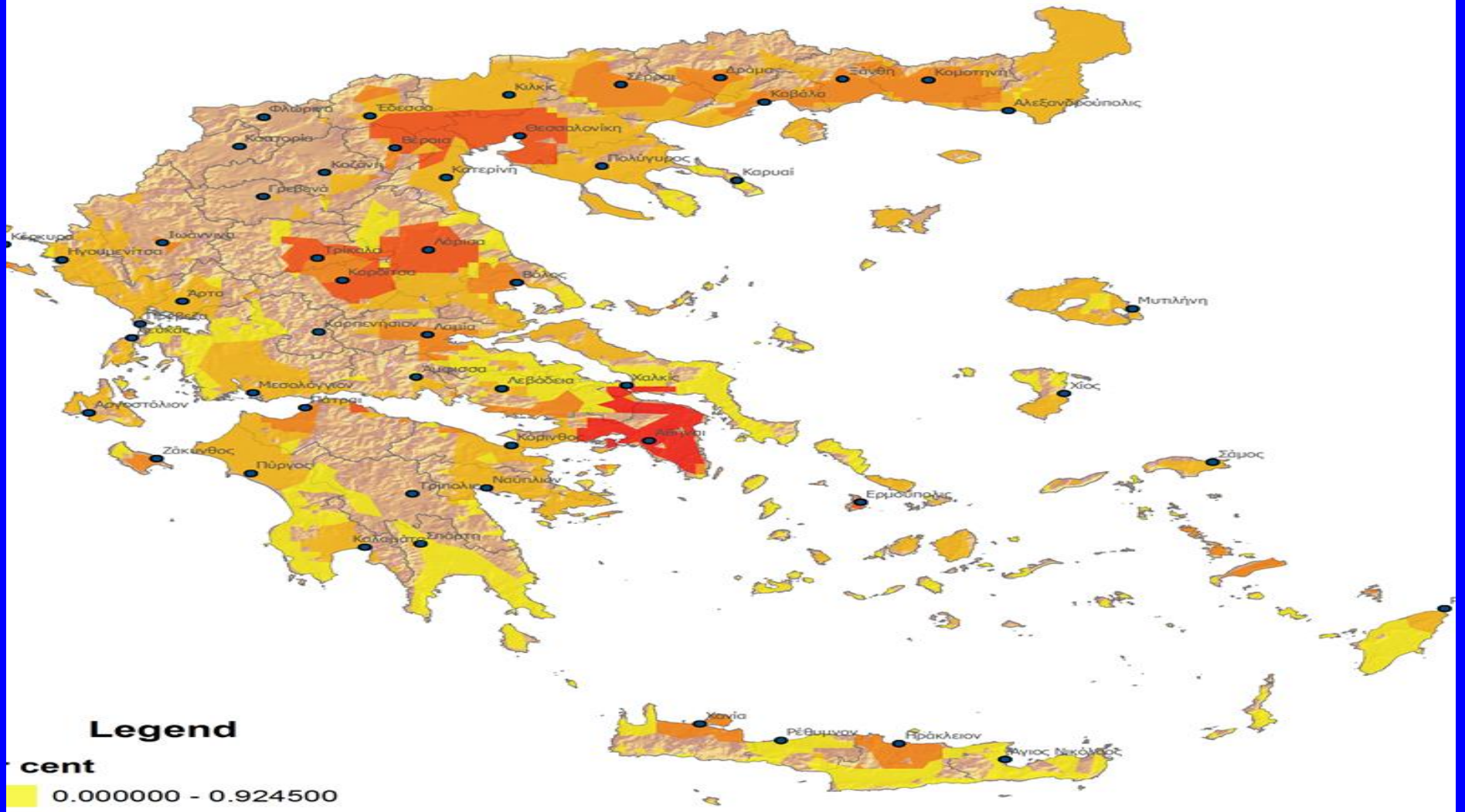
- Mobilization of National Blood Centre and of blood donor associations in the non-affected areas;

- Improvement in the optimal use of blood due to better cooperation between clinicians and blood banks.

Outbreaks affecting the same areas Greece



West Nile Virus Risk Map 2013

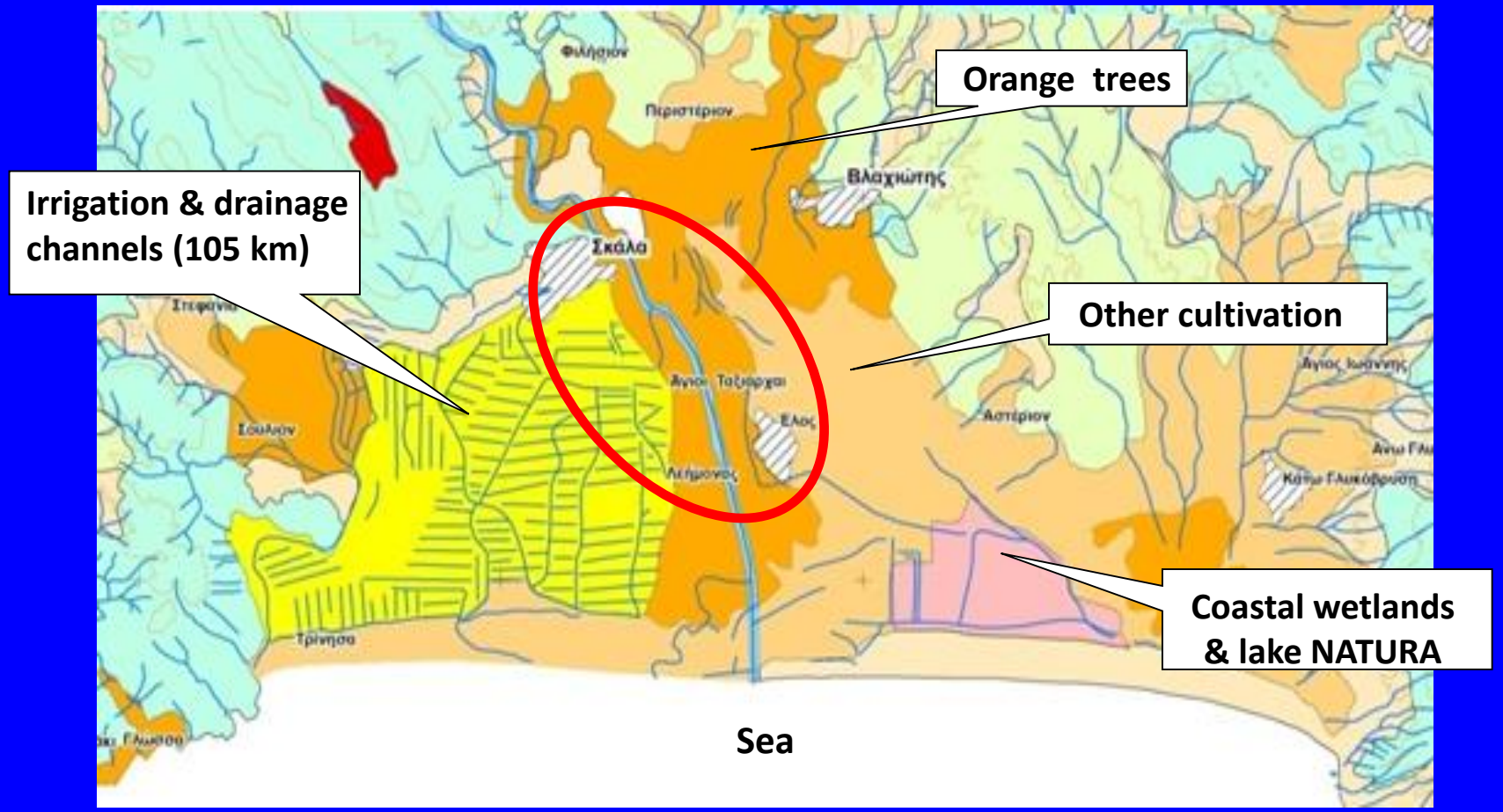


Legend

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- 0.924501 - 1.986000
- 1.986001 - 4.178700
- 4.178701 - 12.371000
- 12.371001 - 25.884200

Land Use Map of Evrotas 2013



Conclusions

- In Europe most malaria cases are imported by travelers from endemic areas,
  but locally acquired transmission is possible due to the presence of competent vectors
- Increasing travelling and **immigration** may significantly augment the risk of malaria in areas currently not affected or re-establish malaria in areas previously affected

- In Greece the implementation of the Action Plan for the prevention and control of Malaria resulted in:
  - Substantial decline of local transmission of malaria in 2013
  - No locally acquired cases in 2014
  - Specific blood safety measures without significant consequences on the blood supply and no TTM cases reported
- Thanks to intensive public health and blood safety and haemovigilance measures the threat of re-establishment of *P. vivax* especially in Lakonia has been managed effectively
- Our experience may provide useful information for other national blood safety authorities in preventing and managing malaria

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ECDC

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