Transfusion transmitted infections in National Haemovigilance Systems: the Greek experience

Global blood product safety

10 April 2019, Rome, Italy

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National Coordinating Haemovigilance Centre

National Public Health Organization (former KEELPNO)

Agenda

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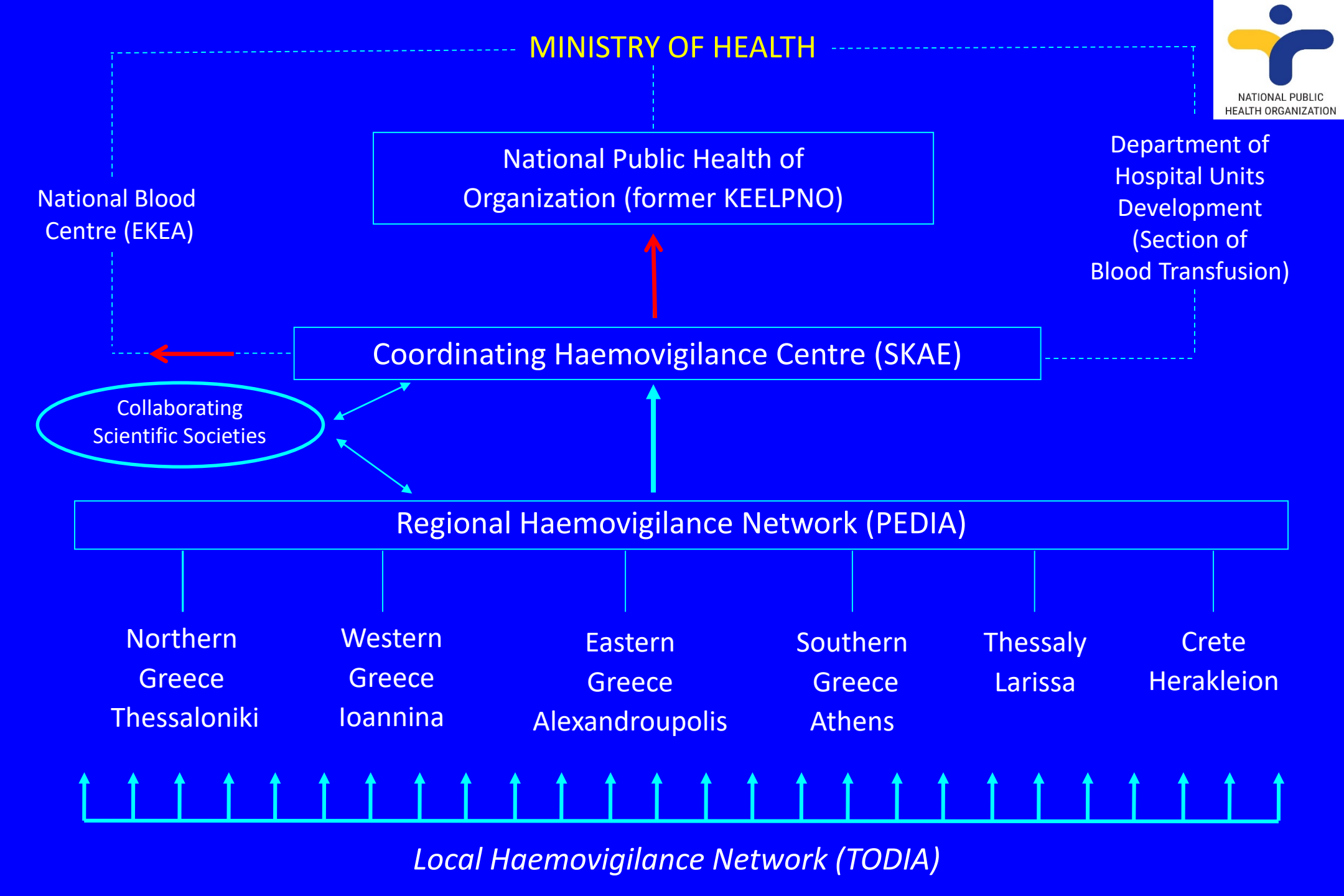
- The National Coordinating Haemovigilance Centre (SKAE)
  - The Network and Basic Activities
  - Working methods
- Surveillance of transfusion transmitted infections:
  - In donor blood
  - In the recipient (the risk of transfusion)
  - Post Donation Information
  - Post Transfusion Information
  - Looking back schemes
- Management of Communicable Diseases Outbreaks (WNV, Malaria..)
- The contribution of SKAE in blood safety
- Conclusions


MINISTRY OF HEALTH
NATIONAL PUBLIC HEALTH ORGANIZATION
National Public Health of Organization (former KEELPNO)
National Blood Centre (EKEA)
Department of Hospital Units Development (Section of Blood Transfusion)
Coordinating Haemovigilance Centre (SKAE)
Collaborating Scientific Societies
Regional Haemovigilance Network (PEDIA)
Northern Greece Thessaloniki
Western Greece Ioannina
Eastern Greece Alexandroupolis
Southern Greece Athens
Thessaly Larissa
Crete Herakleion
Local Haemovigilance Network (TODIA)

SKAE's basic functions

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- Surveillance of transfusion transmissible Infections TTIs
  - Traceability Retrieval of potential infectious donations Look back
- Surveillance of adverse reactions and adverse events associated with blood transfusion
  - Reporting to the competent authorities Recommending preventive and corrective measures Warning BTS and hospitals
    - Informing the medical community about the risk of transfusion
- Surveillance of adverse reactions and events in blood donors during or after donation
  - Alerts Crisis management Cost-effective studies Education Publications

Haemovigilance in Greece
Coordinating Haemovigilance Centre

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Foundation and establishment by KEELPNO Nov. 1995

Legislation in harmonization with

- EU Directives
- Law 3402/2005, Presidential Decree 51/2008
- Ministerial Resolution 261/2011 (articles 1,2,3)

  - Article1 Haemovigilance System

  - Article 2 Notification of adverse reactions /adverse events (ARs/AEs)

  - Article 3

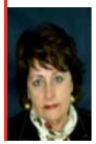
- Working Methods of SKAE
- Corrective and preventive measures (CAPA) are submitted by SKAE to EKEA and EODY (former KEELPNO)

Source: Hellenic Coordinating Haemovigilance Centre

Transfusion Today
Number 107,
June 2016 p20-21

EUROPE

1995-2015: Twenty years of haemovigilance in Greece



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Background
The Coordinating Haemovigilance Centre (abbreviated as SKAE in Greek) was founded by the Hellenic Centre for Disease Control and Prevention (KEELPNO) in November 1995 on a voluntary basis. It was established in line with European National legislation (Min.Res. 261/2011) defines SKAE competence pursuant to European Directives for the development and implementation of the haemovigilance system under the aegis of KEELPNO of the Ministry of Health.

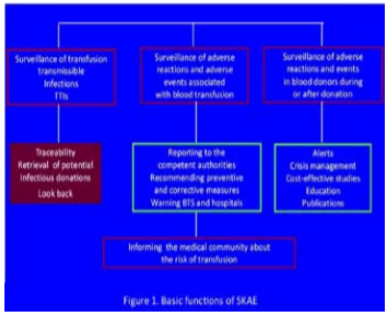

Figure 1. Basic functions of SKAE

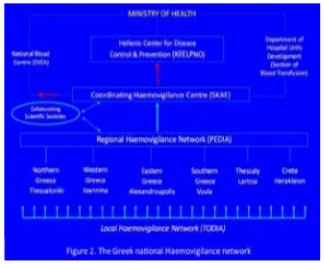

Figure 2. The Greek national Haemovigilance network

Methods
SKAE collects, monitors, and analyses all adverse reactions (ARs) and adverse events (AEs) related to transfusion and donation including epidemiological surveillance of transfusion transmissible infections (TTIs). EU and ISBT/IHN standard definitions maintain homogeneity in reporting and allow benchmarking. Other activities include traceability, look-back, quality management indices, crisis management, cost effectiveness and training *(Figure 1)*.

The haemovigilance system includes networks between hospital clinical departments and hospital blood banks, blood establishments, and the National Blood Centre *(Figure 2)*.

SKAE's action plan has developed towards new activities including haemovigilance for specific patients' groups e.g. thalassaemia, root cause analysis (RCA) and contribution to the development of biovigilance *(Figure 3)*.

Results
Coverage is 93% of total blood units issued for transfusion. In 2014 the incidence of all ARs was 1:460 units of blood components (BCs). Febrile non-haemolytic (45%) and allergic reactions (37%) were commonest. Serious ARs were 1:6,863 units. 34% were attributed to IBCT and 39% were associated with the respiratory track system (TACO 17%, TRALI

EUROPE

Figure 3. Action plan

15% and TAD 7%). Trends over the surveillance period show significantly increased incidence of febrile ARs and TAD, and decrease of IBCT. Nine fatalities were reported: three ABO incompatibility, two TRALI, two bacterial, one TACO, one GvHD.

Two transmissions of HIV from one donor owing to donation during the window period and 54 cases of bacterial infection were recorded. The distribution of ARs by imputability in 2014 was 18% definite, 47% probable, 29% possible and 6% impossible.

- *Incidence of serious* AEs in 2006-2014 was 1:13,368 processed units of BCs. "Near misses" were 1:3,059 units .60% of all AEs are attributed to human error.
- *Blood donation:* the incidence of any AR in 2014 was 1:86 donors (78% vasovagal). SARs were 0.3%.
- *Seroprevalence of infectious markers* (HBsAg, anti-HIV, anti-HCV, Syphilis and anti-HTLV) in donor blood in 1996-2014 totalled 0.32 % (Figure 4). Rates stabilized in 2008-2014 NAT yields for HIV-RNA, HCV-RNA, HBV-DNA in 2007-2014 were 1:391,255, 1:195,628 and 1:8,325, respectively. WNV-RNA in 2010 – 2014 was 1:11,289.

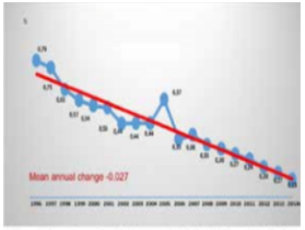

Figure 4. Seroprevalence of total infectious markers in 10,001,525 tested blood units

Conclusions/Recommendations
Twenty years of haemovigilance in Greece demonstrate coordinated progress towards better quality and safety in blood donation and transfusion.

However, the prevalence of TTIs remains relatively high especially regarding HIV and occult HBV. At the same time notable progress in the implementation of NAT screening for HCV-RNA, HIV-RNA and HBV-DNA as well as for WNV-RNA seasonal screening has led to significant advances in assuring blood safety.

The frequency of transfusion of wrong blood to the wrong patient due to pre-marked sampling tubes and failure to verify identity of the patient in the clinical environment has been declining over the second decade of the surveillance period, however IBCT remains one of the most important adverse events attributed mainly to human error.
Implementation of patient identification system and full computerized record – keeping in blood services and clinical departments as well as universal application of pre-storage leukodepletion and use of pathogen reduction technologies are recommended for the avoidance of adverse reactions in transfusion.

Continuous nursing and medical supervision during donation and management of complications especially vagovasal reactions and injury by the needle will contribute greatly to safeguarding the well-being of our donors and ensure their willingness to be retained as regular donors.

2010- 2017 Seroprevalence in 4.341.232 blood units
Mean annual change

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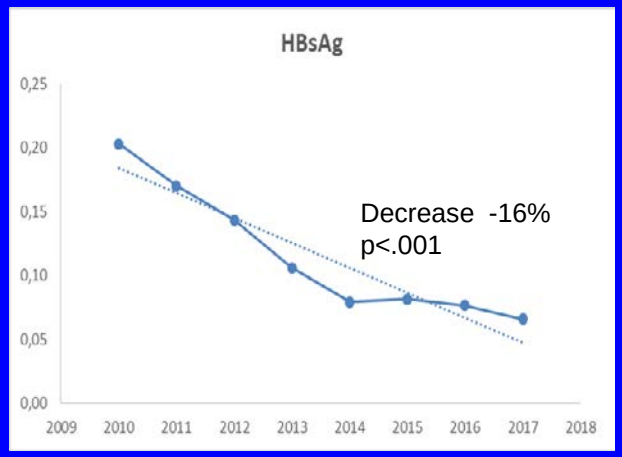

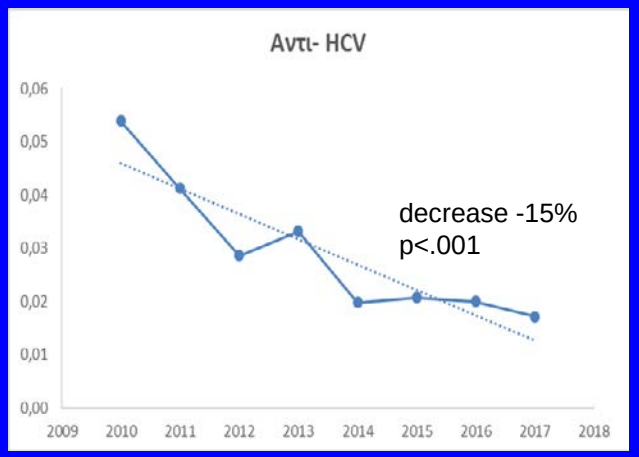

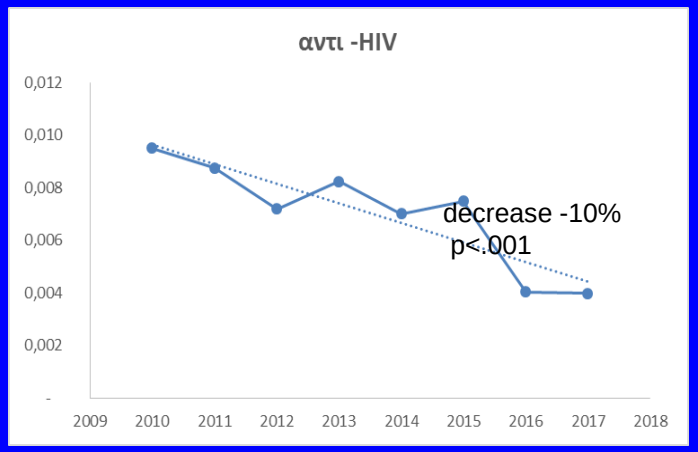

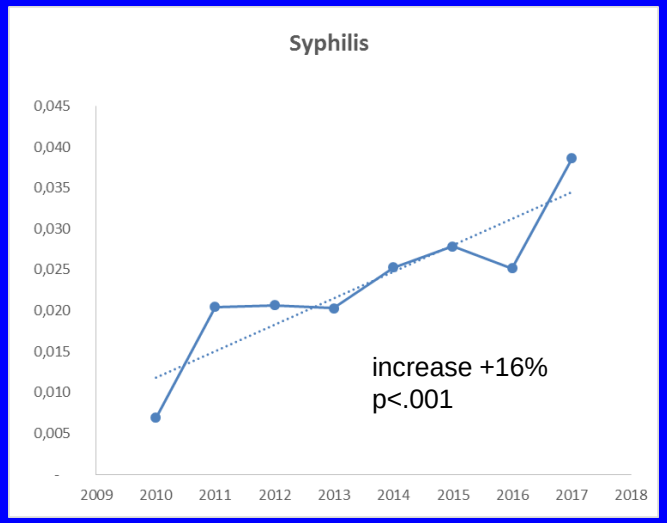

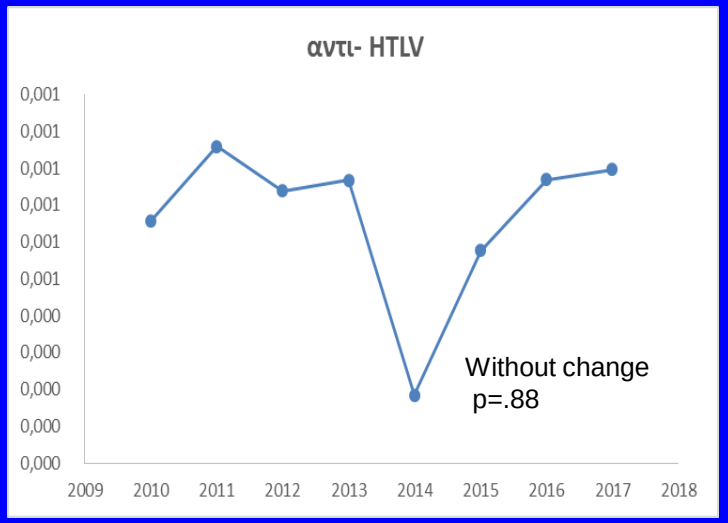

Reduction in the total number of TTIs -12%, p<0.001

Total rate 178.5 / 100,000

Source: Hellenic Coordinating Haemovigilance Centre

Epidemiological Surveillance of TTIs in donor blood 2010-2017

Infections	Rates	
HBs Ag	• 2010: **203.2:100,000 blood units** • 2017: **65.9 : 100,000 blood units**	Reduction -16% p< 0.001
Αντί- HCV	• 2010: **50.2 : 100,000 blood units** • 2017: **17 : 100,000 blood units**	Reduction -15% p< 0.001
Αντί- HIV	• 2010: **9.5 : 100,000 blood units** • 2017: **4 : 100,000 blood units**	Reduction -10% p< 0.001
Αντί- HTLV	• 2010: **0.66 : 100,000 blood units** • 2017: **0.8 : 100,000 blood units**	No change p=0.88
Syphilis	• 2010: **6.9 : 100,000 blood units** • 2017: **38.6 : 100,000 blood units**	Increase +16% p< 0.001

Source: Hellenic Coordinating Haemovigilance Centre

NAT Yields 2007-2017
n=772 blood units (*1.764 blood components*)

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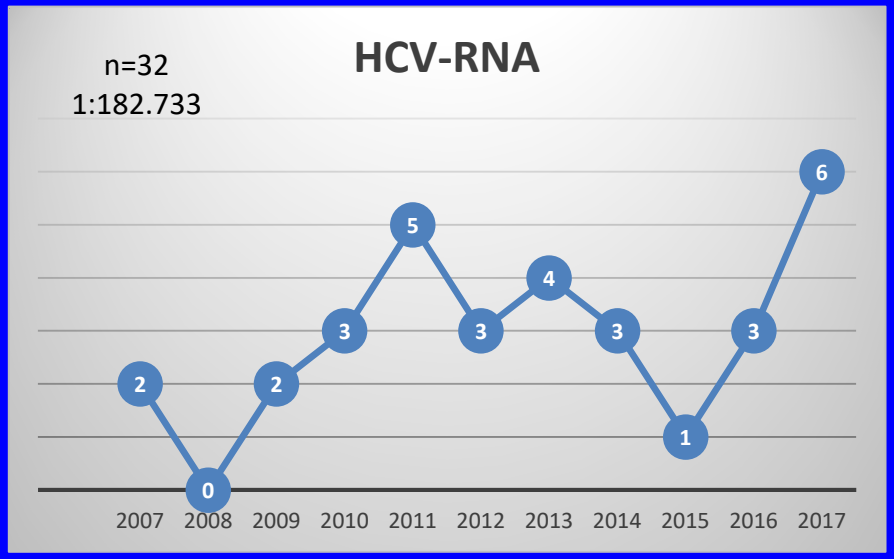

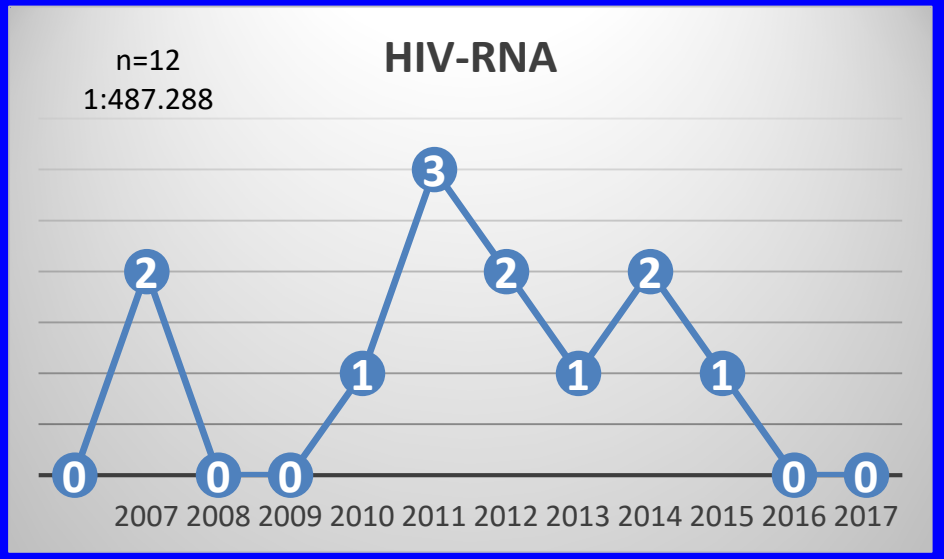

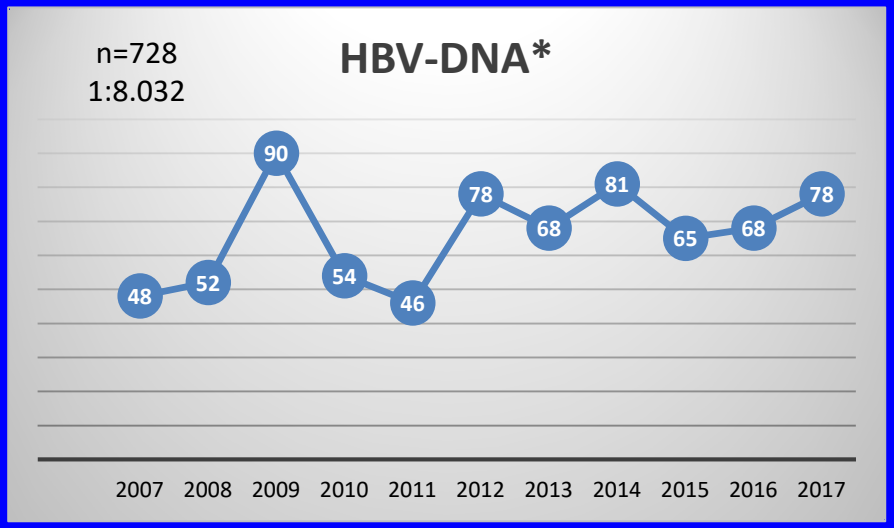

Source: Hellenic Coordinating Haemovigilance Centre

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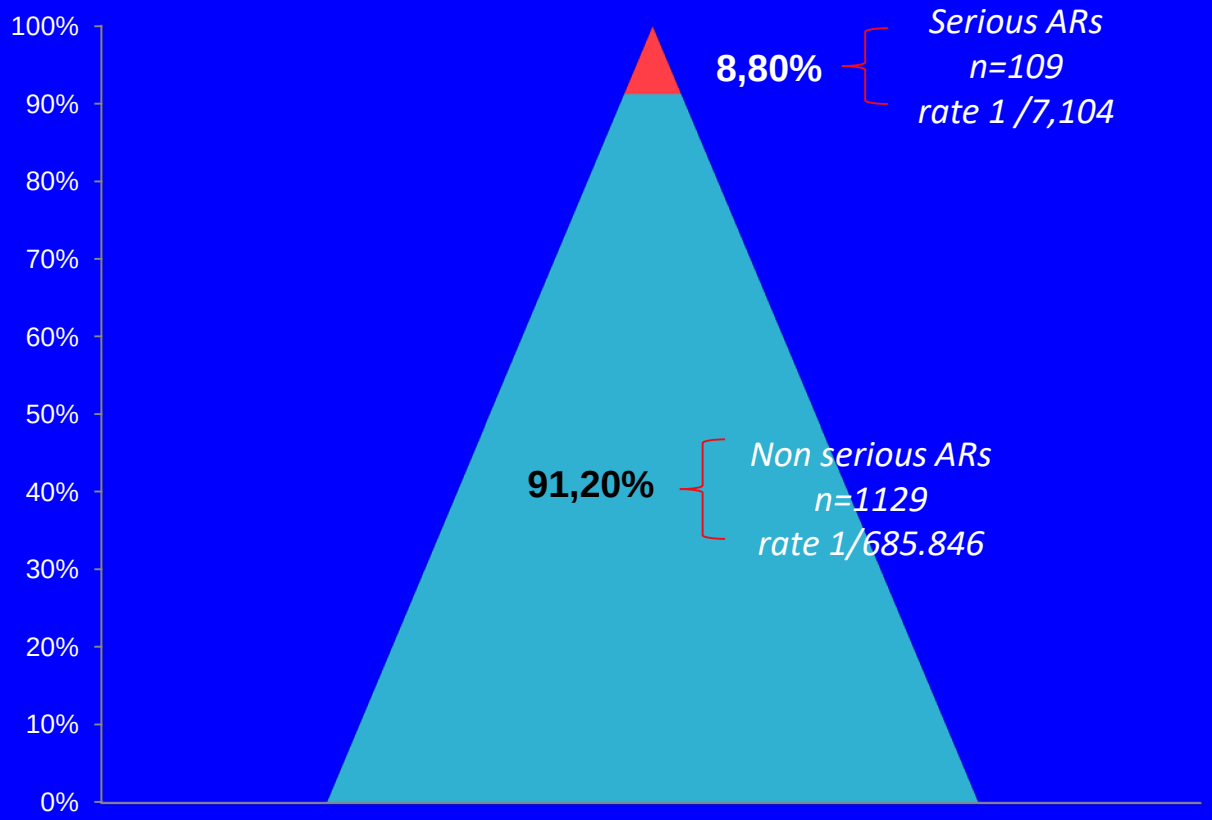
NAT YIELD 2007-2017									
Year	**Blood units tested**	**HIV-RNA**		**HCV-RNA**		**HBV-DNA**		**Total**	**Total Frequency**
			Frequency		Frequency		Frequency	n	
2007	355.214	2	177.607	2	177.607	48	7.400	52	1:6.831
2008	568.210	0	0	0	0	52	10.927	52	1:10.927
2009	582.808	0	0	2	291.404	90	6.476	92	1:6.335
2010	609.735	1	609.735	3	203.245	54	11.291	58	1:10.513
2011	582.187	3	194.062	5	116.437	46	12.656	54	1:10.781
2012	542.240	2	271.120	3	180.747	78	6.952	83	1:6.533
2013	521.750	1	521.750	4	130.438	68	7.673	73	1:7.147
2014	541.662	2	270.831	3	180.554	81	6.687	86	1:6.298
2015	520.844	1	520.844	1	520.844	65	8.013	67	1:7.773
2016	520.501	0	0	3	173.500	68	7.654	71	1:7324
2017	502.313	0	0	6	83.719	78	6.440	84	1:6196
Total	**5.847.464**	**12**	**487.289**	**32**	**182.733**	**728**	**8.032**	**772**	**7574**

Referring to 1.764 blood components that didn't used

Source: Hellenic Coordinating Haemovigilance Centre

Frequency of Adverse Reactions in 774,321 issued blood units 2017

All ARs n=1238
rate1/625.46



HAEMOVIGILANCE DATA: **the recipient**

Source: Hellenic Coordinating Haemovigilance Centre

Haemovigilance Data 2010-2017

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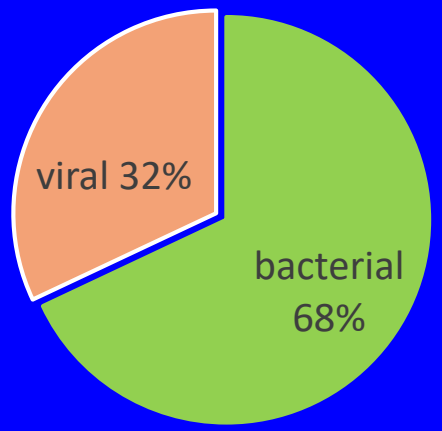
- Blood components Issued 5,981,777
- All Adverse reactions 10,597

  Rate 17.7/100,000 units (1:565)

- TT- ARs
  - **TT- Bacterial** **n= 17**
    - Serratia Marcessens 2
    - Citrobacter Loseri 1
    - Klebsiella 1
    - Staph. Aureus 4
    - Occult Bacteraemia 3
    - Undetermined 4
    - Unsuitable samping 2
  - **TT- Viral** **n= 8**
    - HBV 3
    - HCV 2
    - WNV 2
    - HEV 1



Total n= 25 : 5,981,777
rate 1:239,271
0.4/100,000 blood units

Source: Hellenic Coordinating Haemovigilance Centre

Infectious Risk of Transfusion 2010-2017

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Year	2010	2011	2012	2013	2014	2015	2016	2017	Total
All ARs	1048	1062	1235	1282	1612	1570	1332	1456	10,597
Issued Blood Components	777,613	714,543	737,247	729,529	720,574	768,672	759,278	774,321	5,981,777
Bacterial	2	7	1	0	3	3	0	1	17 (68%)
Viral	0	1	1	1	1	1	2	1	8 (32%)
Parasitic	0	0	0	0	0	0	0	0	0
Total	2	8	2	1	4	4	2	2	25 (100%)

All infectious ARs 0.24% of total ARs

Rates

0.4 /100,000 issued blood components

Source: Hellenic Coordinating Haemovigilance Centre

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Infectious ARs by imputability level

Levels	Bacterial	Viral	Total
1 Not determined	4	2	6
2 Possible	6	1	7
3 Probable	3	1	4
4 Certain	4	4	8

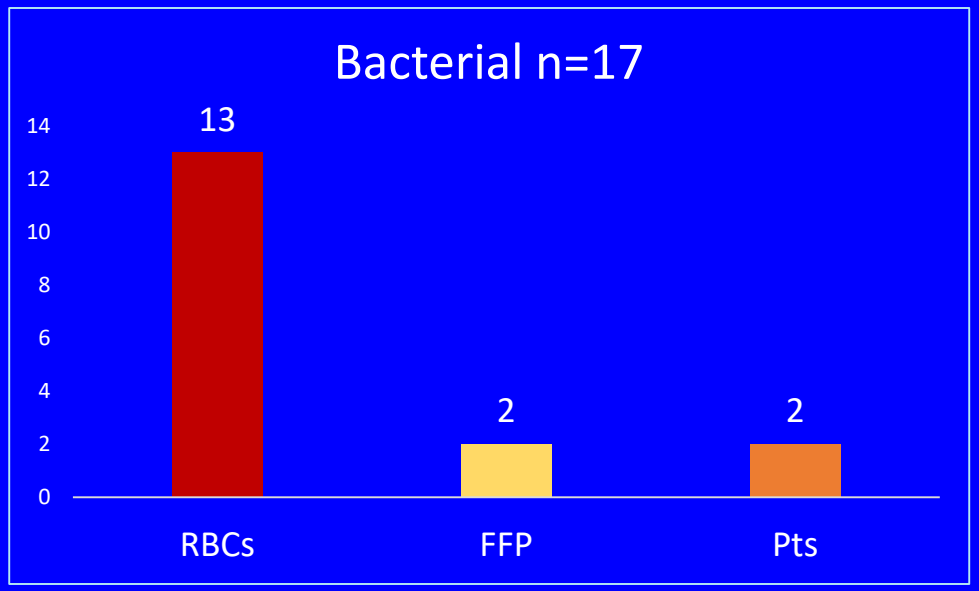
Infectious ARs by severity level

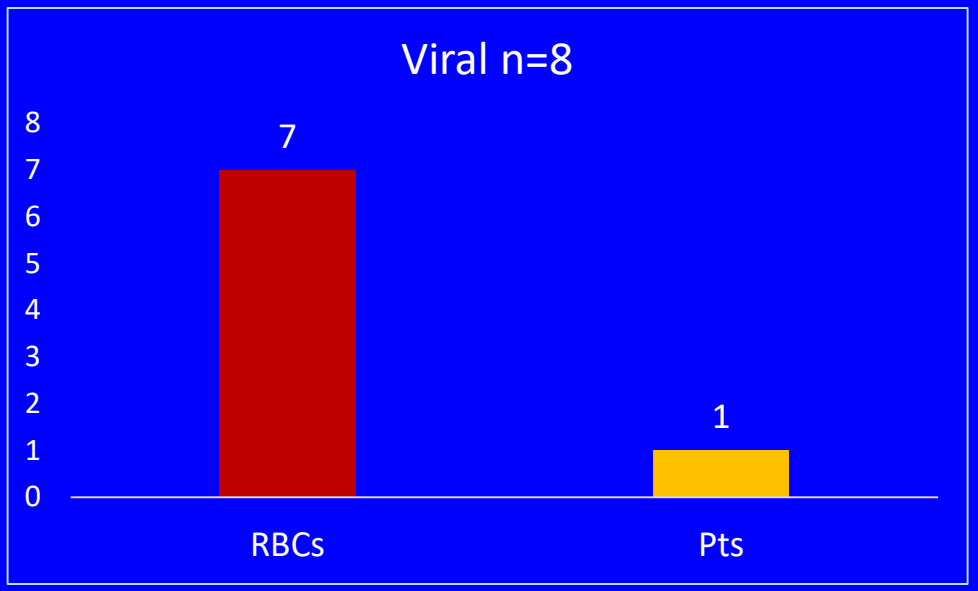
Grade	Bacterial	Viral	Total
1 Non serious	6	2	8
2 Serious	8	4	12
3 Life threatening*	1	2*	3
4 Death**	2	0	2

* 1 TT- WNVD case associated to Aphaeresis Platelets in 2012
1 TT- HEV case associated to RBCs
**2 TT- Serratia Marcessens cases associated to RBCs in 2012 and Aphaeresis Platelets in 2014

Source: Hellenic Coordinating Haemovigilance Centre

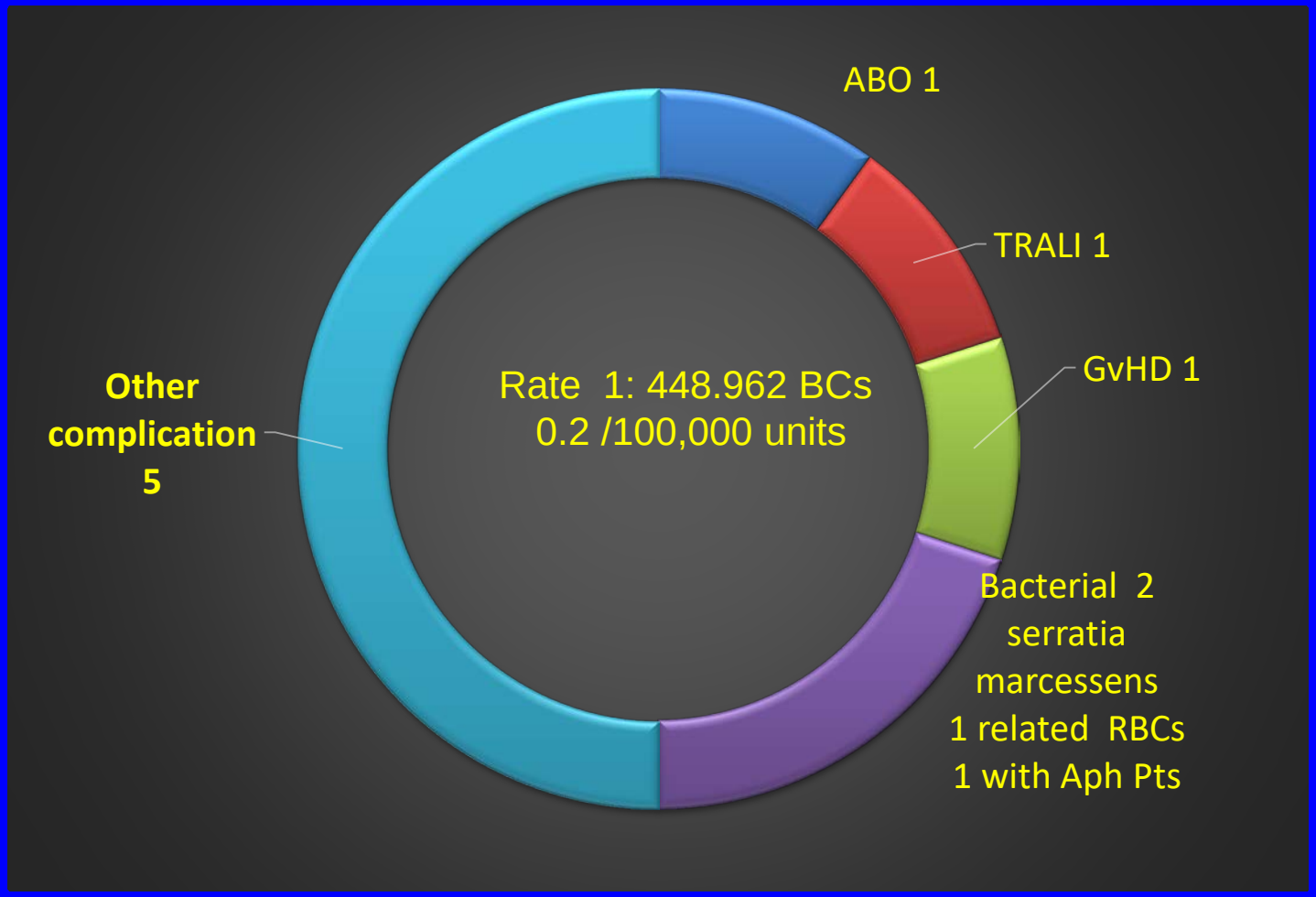
Infectious ARs per blood component





Source: Hellenic Coordinating Haemovigilance Centre

All Fatalities
4.489.621 blood components, 2012-2017 n=10



Source: Hellenic Coordinating Haemovigilance Centre

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Emerging Infectious Diseases in Greece

Malaria

WNV

New and emerging infectious agents

- The spread of insect vectors through travel and trade combined with climate change pose a significant challenge for public health and transfusion medicine in European and other countries

  Malaria, WNV, Dengue virus, Babesiosis, Q Fever, the Chikungunya virus, Chagas disease are examples of such infectious diseases

  - Donor deferral may not be an option in the newly affected areas
  - Donation testing is then the main tool to reduce the risk of transmission
  - Pathogen reduction for FFP and Platelets may also be considered

Source: Hellenic Coordinating Haemovigilance Centre

Transfusion Transmission Attributes

- Presence of the agent in blood during an asymptomatic phase in donor
- The agent's survival /persistence in blood during processing / storage/ distribution
- Recognition of agent as responsible for a clinical apparent outcome in a least a proportion of recipient(s)who become infected

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- For EID agents, the response with respect to blood safety varies in relation to the severity of the agent, its incidence and prevalence/rate of emergence

Stramer SL et al. Transfusion 2009;49
Stramer SL, Dodd RY Transfusion 2013; 53

Theraflex Methylene Blue treated including the Blueflex System					Quarantine Plasma			
Year	Units	Patients	Total Transfusion Adverse Reactions	SARs	Total Units	Total patients	Total ARs	SARs
2001-2011	73,778	1.920	n=3 rate 1:24,593 0,4/10,000 3 Allergic, severity grade 1 rate 1:24,593 0,4/10,000 **MB-FFP vs Q-FFP** **1:24,393/1:3,620** **P<0.001**	n=0	217,173	12,085	n=60 rate 1:3,620 2,8/100,000 Allergic 29 FNHTR 18 TRALI 3 TAD 1 TACO 1 Bacterial 6 Other 1	n=16 rate 1:13,573 0,7/100,000 Allergic 8 FNHTR 3 TRALI 1 TAD 1 Bacterial 3
International Prospective Haemovigilance Study on MB-treated Plasma								
May 2014-April 2015	9,241	1,234	0	0				
Total	83,019	3,154	3	0				

C. Politis, L. Kavallierou et al Transfusion Medicine 2014,24,316-320
L.,Noens ,A. Megalou et al Vox Sanguinis 2017

PI in aphaeresis platelets in Greece

Use of MIRASOL Pathogen Reduction Technology

- 2009-2018

Treated units n= 6560, Patients n=2,887

Adverse transfusion reactions

1 mild allergic reaction (Incidence 1.5/10.000 units)

The patient had history of allergic reactions associated with other non-treated products

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A study on cytokines and other biological modifiers in platelets is in process by 4 blood services in cooperation with haematology and oncology departments

O. Katsarou, A. Athanasopoulos, E. Grouzi, A. Tsantes
under publication

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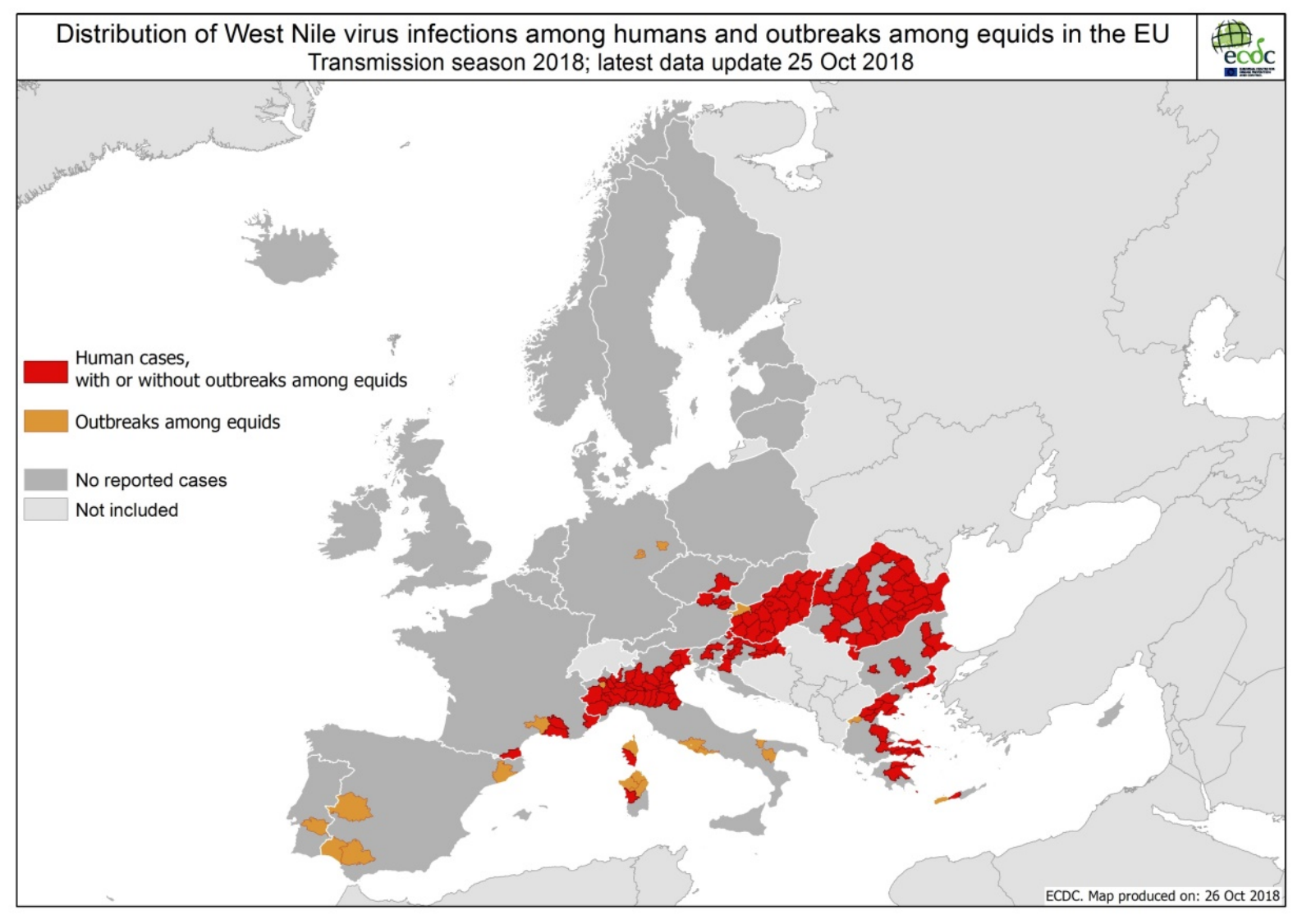
WNV infection

Distribution of WNF cases in humans by affected areas, EU/EEA MS and neighboring countries, 2017 and previous transmission seasons (2011-2018)



Source: ECDC

Proportional distribution of West Nile Virus infection human cases and introduced malaria cases per Regional Unit of exposure, Greece, 2018

(source: National Public Health Organization/ former KEELPNO)

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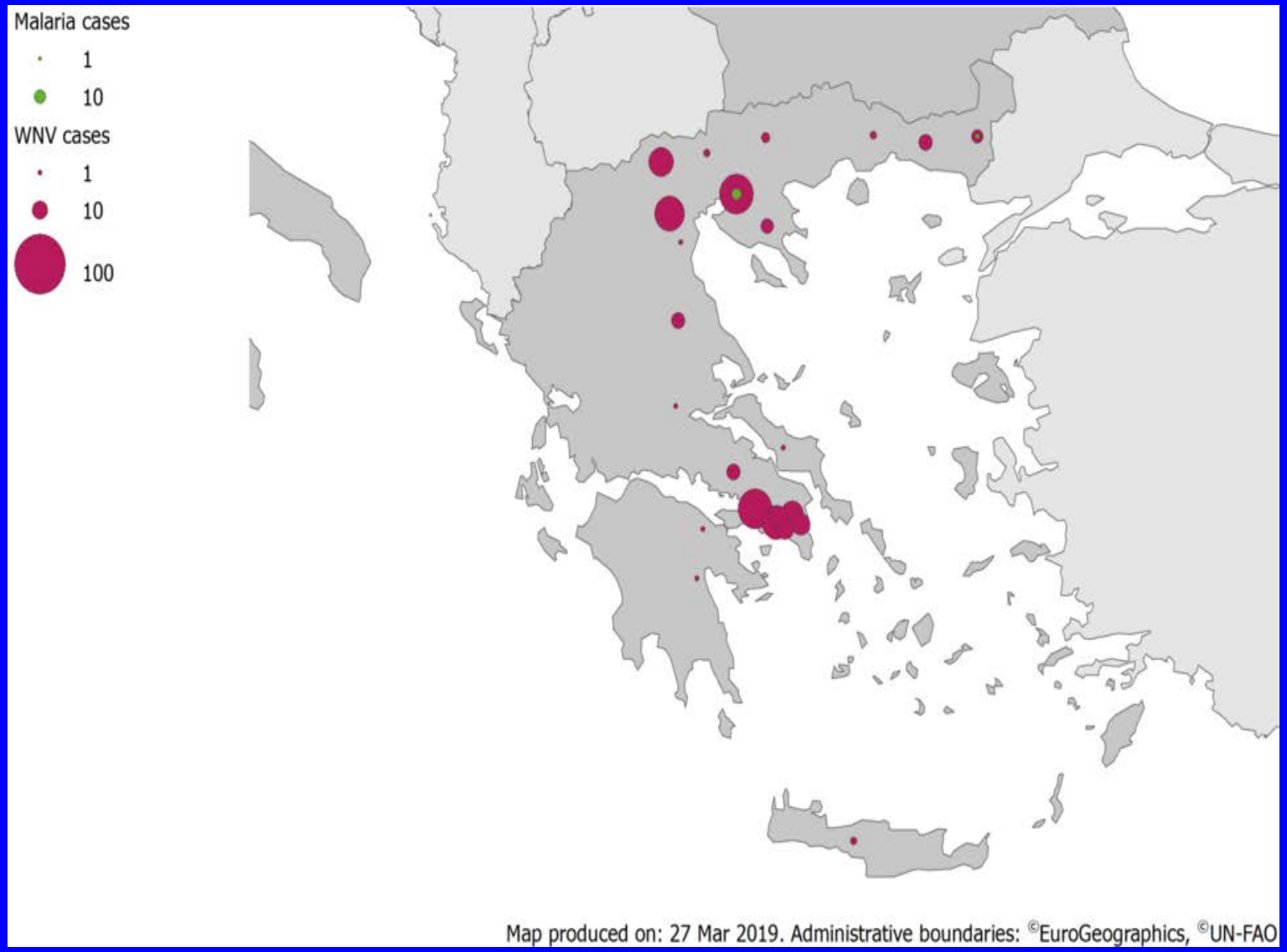

Ten introduced malaria cases were recorded in three Municipalities, also affected by WNV

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WNV-2 cases in Greece 2010-2018

Cases	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
WNND	197	76	109	51	14	0	0	28	243	718
Mild	70	25	52	35	1	0	0	20	73	276
Total	267	100	161	86	15	0	0	48	316	994
Deaths	32	8	16	10	6	0	0	5	50	127
Fatality rate (% WNND)	17	10.5	14.7	19.6	40	0	0	10.4	15.8%	12.8%

Source: National Public Health Organization (former KEELPNO)

Surveillance of Donor Blood WNV-RNA, 2010-2018

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Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	Total
Blood units	27,108	105,610	36,911	26,910	6,662	-	-	3,779	160,097	367,077
Tested with Procleix-WNV ID- NAT	27,108 (100%)	64,910 (61.5%)	28,205 (76.4%)	11,882 (36%)	6296 (94.5%)				155,950 (97%)	294,351 (80.2%)
Tested with Roche Cobas Taqscreen WNV	0	40,700 (38.5%) (in ID-NAT)	8,706 (23.6%) (in MP6)	15,028 (64%)	366 (5,5%)	-	-	3,779 (100%)	4,147 (3%)	72,726 (19.8%)
Donors WNV RNA(+)	8	5	4	1	0	-	-	0	11	29
Prevalence per collected units	1:3,389 2.95/10,000	1:21,122 0.47/10,000	1:9,228 1.08/10,000	1:26,910 0.37/10,000	0 0	- -	- -	0 0	1:15,460	1:12,658 0,8/10,000

Source: Hellenic Coordinating Haemovigilance Centre

TT-WNV in two recipients of blood components derived from the same untested blood unit in Attiki, 2012

- Recipient of Whole Blood Derived Platelets
- Female with AML developed severe WNV encephalitis associated with the transfusion of 1 unit of untested whole blood derived Pts The diagnosis of WNND was established on the basis of serological testing of the patient 12 days after transfusion of the implicated unit. NAT testing of the archived samples of 53 donations transfused in this patient during a period of six weeks prior to the onset of WNND, confirmed the route of transmission through the transfusion of 1 unit of WNV infected Pts

Clinical outcome: the patient remained paraplegic and blind

- Recipient of Plasma

A female 87 years of age suffering from liver cirrhosis was transfused with 1 unit of plasma prepared from the same infected blood unit. The patient did not present any WNV symptoms but ID-NAT testing showed positive results until 15 days post transfusion

- The RBCs unit was recalled
- The implicated donor

Asymptomatic male donor, resident in Attiki, gave blood 9 days before the first WNV case was reported by the Hellenic CDC and the implementation of NAT screening of blood. Retrospective testing of the stored blood sample was positive for WNV-RNA

Source: Hellenic Coordinating Haemovigilance Centre

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Malaria

The History of Malaria in Greece

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- 1975 – 2008
  - 1,419 laboratory-confirmed malaria cases were diagnosed by MRL
  - 20 - 50 imported cases reported annually, the majority travel-related. Another 5 were introduced sporadic cases without travel history: 1991, 1999, 2000 *(Vakali A., Patsoula E., et al Eurosurveillance 2012 :17)*

Haemovigilance data before 2008

- TTM caused by P. malariae in 3 patients with surgery, lymphoma and gastrointestinal bleeding respectively
- In the first case the implicated donor was a Greek female born in an African previously endemic area, who reported having had fever of unknown origin in 1945. A high malarial antibody titre was detected by IFAT, while parasites were not present on blood smears. The interval between acquisition of the infection and malaria transmission via transfusion was probably 48 years.
- Look back studies were not possible for the other two cases

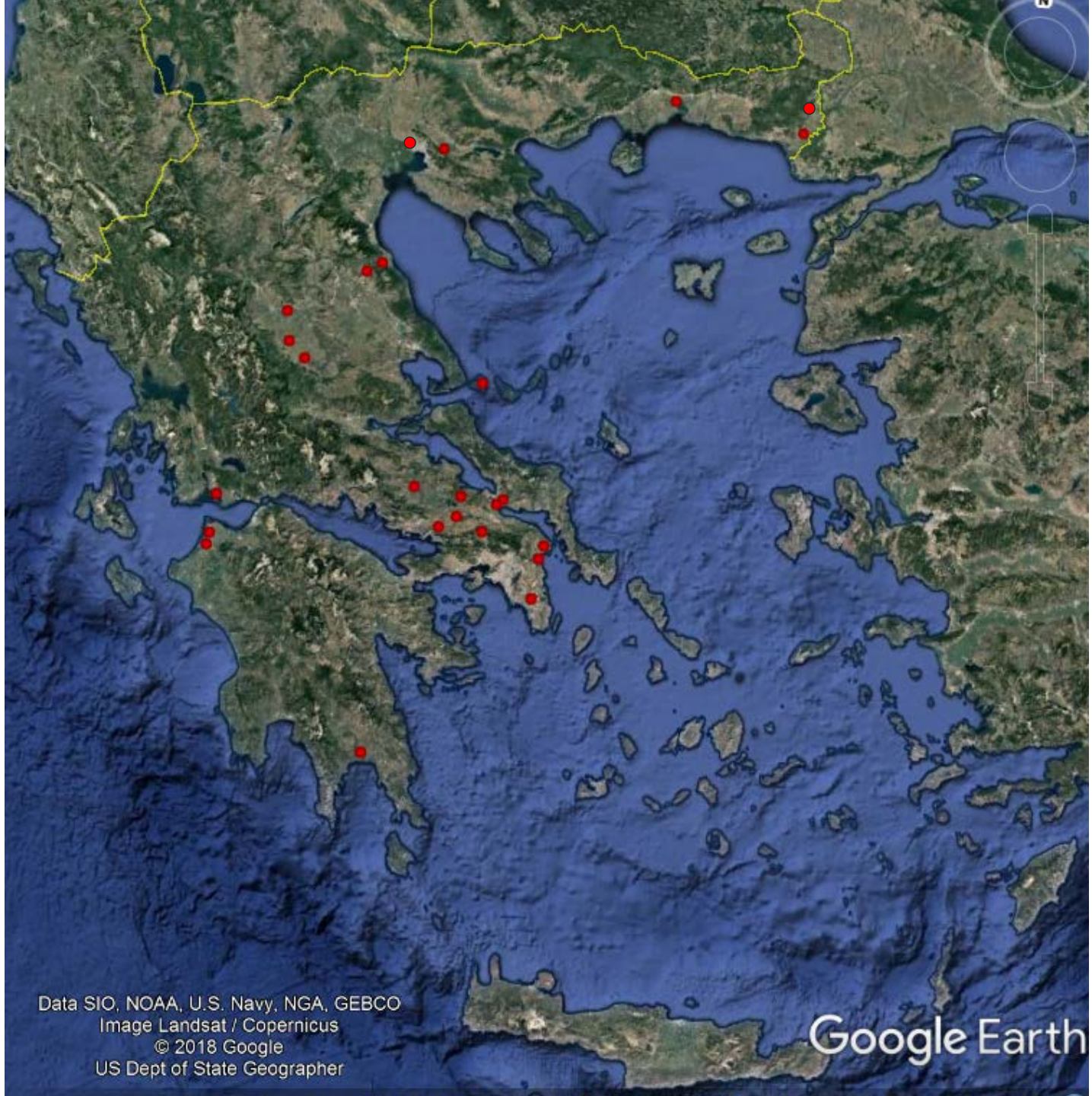
(Tzanetou K, Politis C, Council of Europe Workshop on Haemovigilance and blood Safety, 2007, Greece)

- 2009 -2018

- 20-110 imported cases annually
- A cluster of locally acquired P. vivax malaria in Lakonia (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

Source: Hellenic Coordinating Haemovigilance Centre



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Areas with ≥1 locally acquired/ introduced *P.vivax* malaria case, Greece, 2009-2018 (n=25)

Source: National Public Health Organization/ former KEELPNO

data under publication

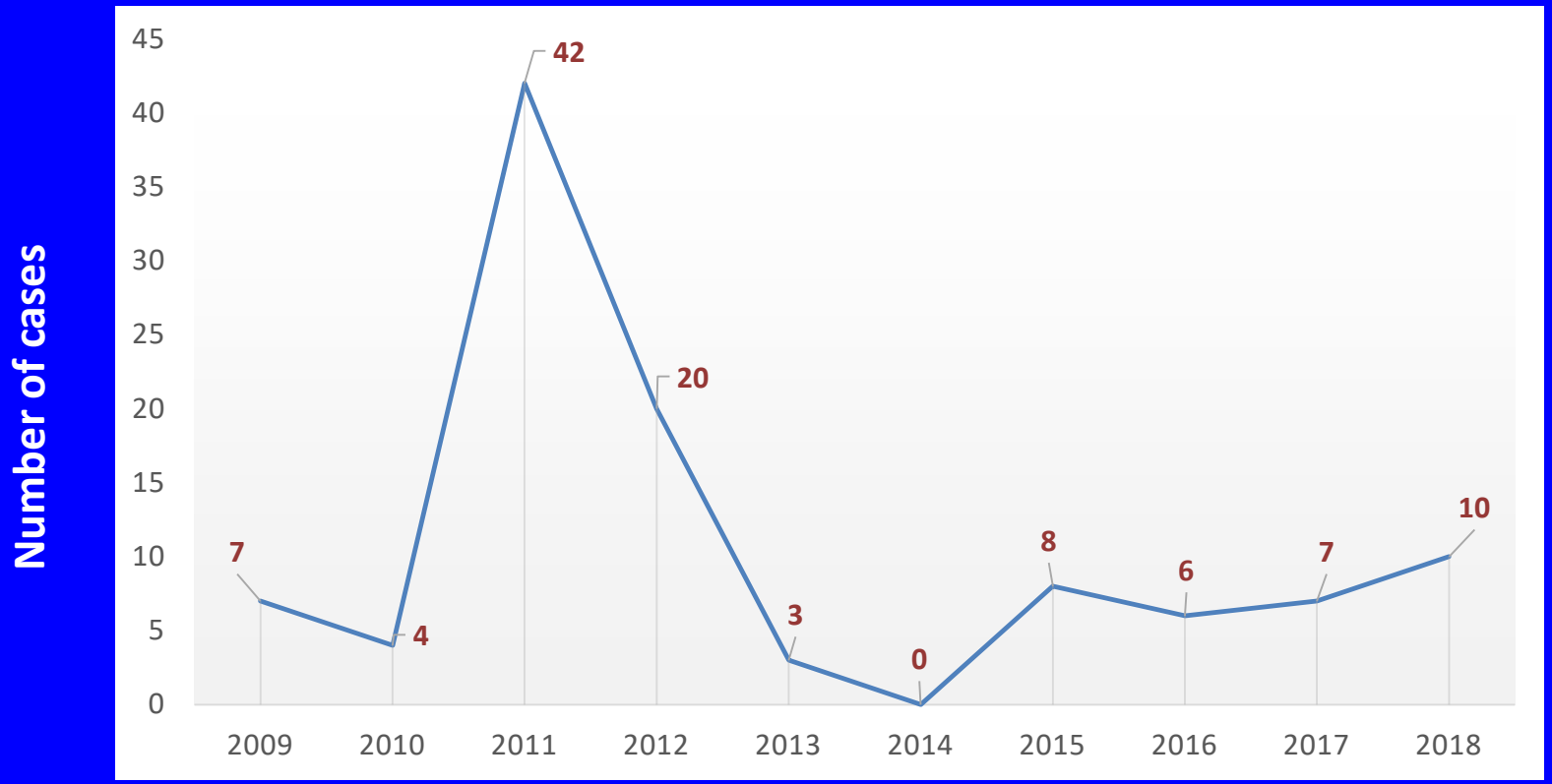
Reported malaria cases by year and case classification, Greece, 2009-2018

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	8	87
2016	111	6	117
2017	100	7	107
2018	44	10	54
Total	**605**	**109***	**714**

*Additionally: 2 cases of unknown classification

Source: National Public Health Organization (former KEELPNO)

Locally acquired malaria cases by year of infection, Greece, 2009 – 2018*



*Since 2013 all cases were introduced

Source: Hellenic Coordinating Haemovigilance Centre

Selective blood donation screening for evidence of malaria in affected areas , 2009-2018**

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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

** In 2016-2018 no selective blood donation screening was performed

Source: Hellenic Coordinating Haemovigilance Centre

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Conclusions

- Advanced donor selection policies and blood screening have considerably minimized the infectious risk of transfusion in the recipient
- However some emerging infectious diseases represent an increasing threat to the safety of blood
- Pathogen reduction in blood components maybe considered by National Authorities as a future strategy to safeguard blood safety

  For this purpose a risk / benefit analysis should be carried out on a country by country basis

Thank you
for your attention