

Malaria / Babesia in Europe

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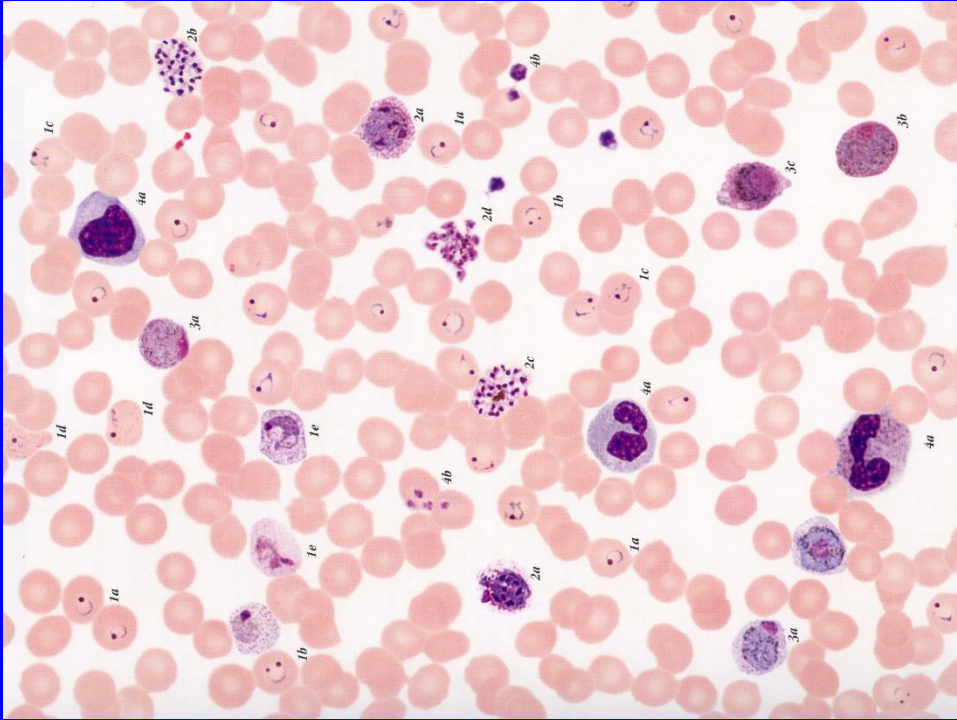
Coordinating Haemovigilance Centre and Surveillance of Transfusion
(SKAEM)

Greece

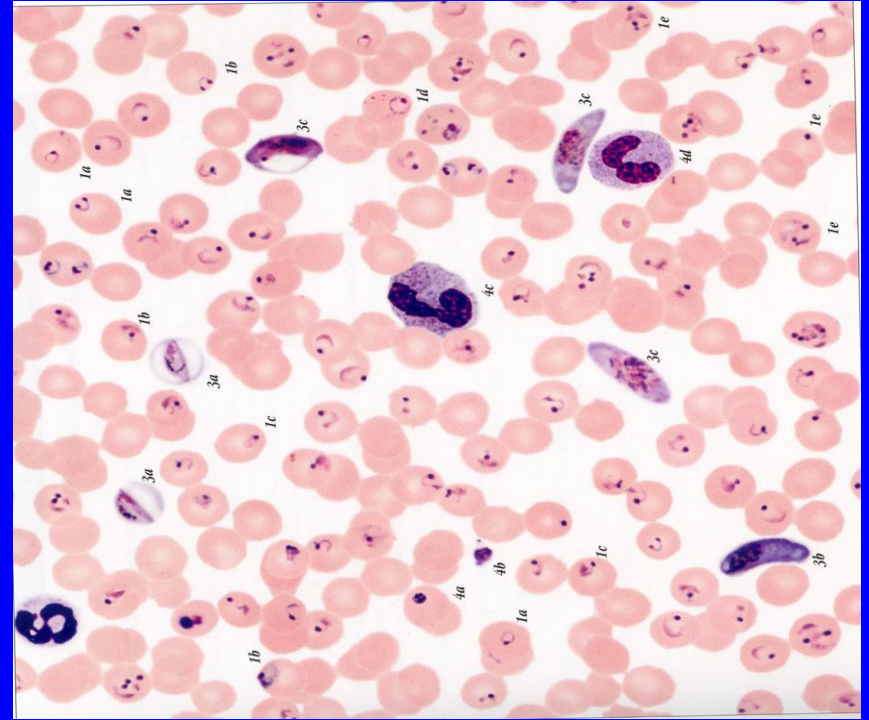
28th IPFA/PEI workshop

Porto, 2022

Malaria



Plasmodium vivax



Pasmodium falciparum

Disease background information

- Malaria is a protozoan parasitic infection in humans resulting from infection of one or more of the five species of the genus Plasmodium:
P. falciparum, *P. vivax*, *P. ovale*, *P. malaria* and *P. Knowlesi* transmitted by *Anopheles* mosquitoes
- Among P. parasites, *P. falciparum* can lead to life- threatening infection and is the most prevalent malaria parasite on the African continent
- In addition, *P. Vivax* can lead to malaria relapses and commonly infects humans in many countries outside the sub-Saharan Africa
- WHO estimates that 3.3 billion of the world's population resides in malaria -endemic regions, and of those, 1.2 billion are at high risk of malaria infection.
Malaria often affects the most vulnerable, notably young children and pregnant women in the developing world, leading to significant morbidity and mortality

All EU Member States are considered free of *P.falciparum* and *P.vivax* malaria

The most ancient genetic evidence of malaria



Tutankhamun 1341 -1323 BC 18ⁿ Dynasty

Malaria in Europe

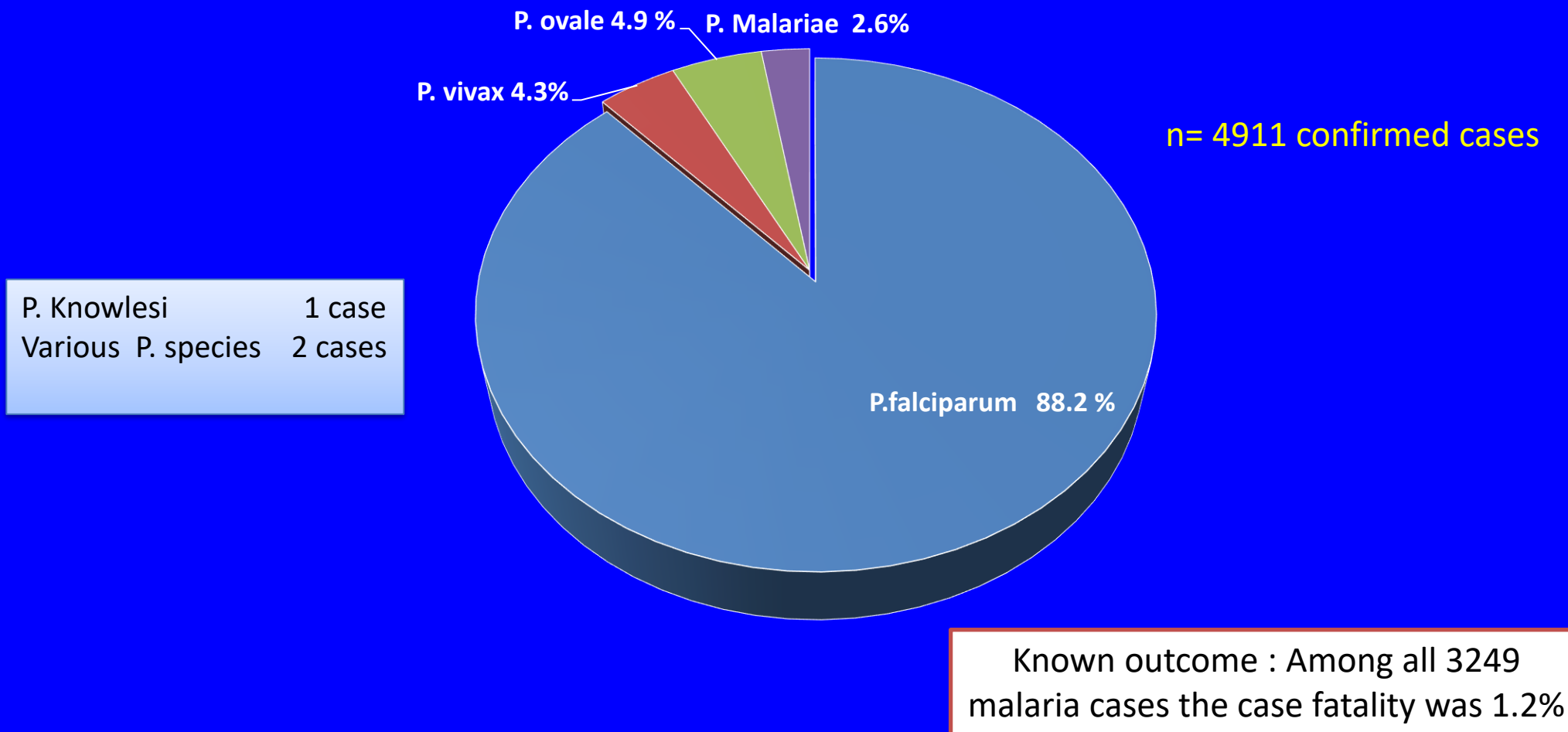
(ECDC Surveillance Report for 2019)

- Malaria is a notifiable disease in EU
- The EU case definition requires the presence of fever or a history of fever, and the presence of parasites detected in a blood film or the detection of Plasmodium nucleic acid or Plasmodium antigens in blood
- For 2019, in the EU/ EEA countries, 8641 malaria cases were reported, of which >99% were confirmed
 - 99,8% were travel-related. Nine confirmed cases were reported as acquired in the EU (two each by Germany, Greece, Spain and France and one by the Netherlands)
 - A marked seasonal trend was observed across all countries, with cases increasing during and immediately after the summer holiday months (July-September)
 - France reported the highest number of cases, followed by the UK and Germany

Overall Notification Rate:
1.3 cases / 100,000 population

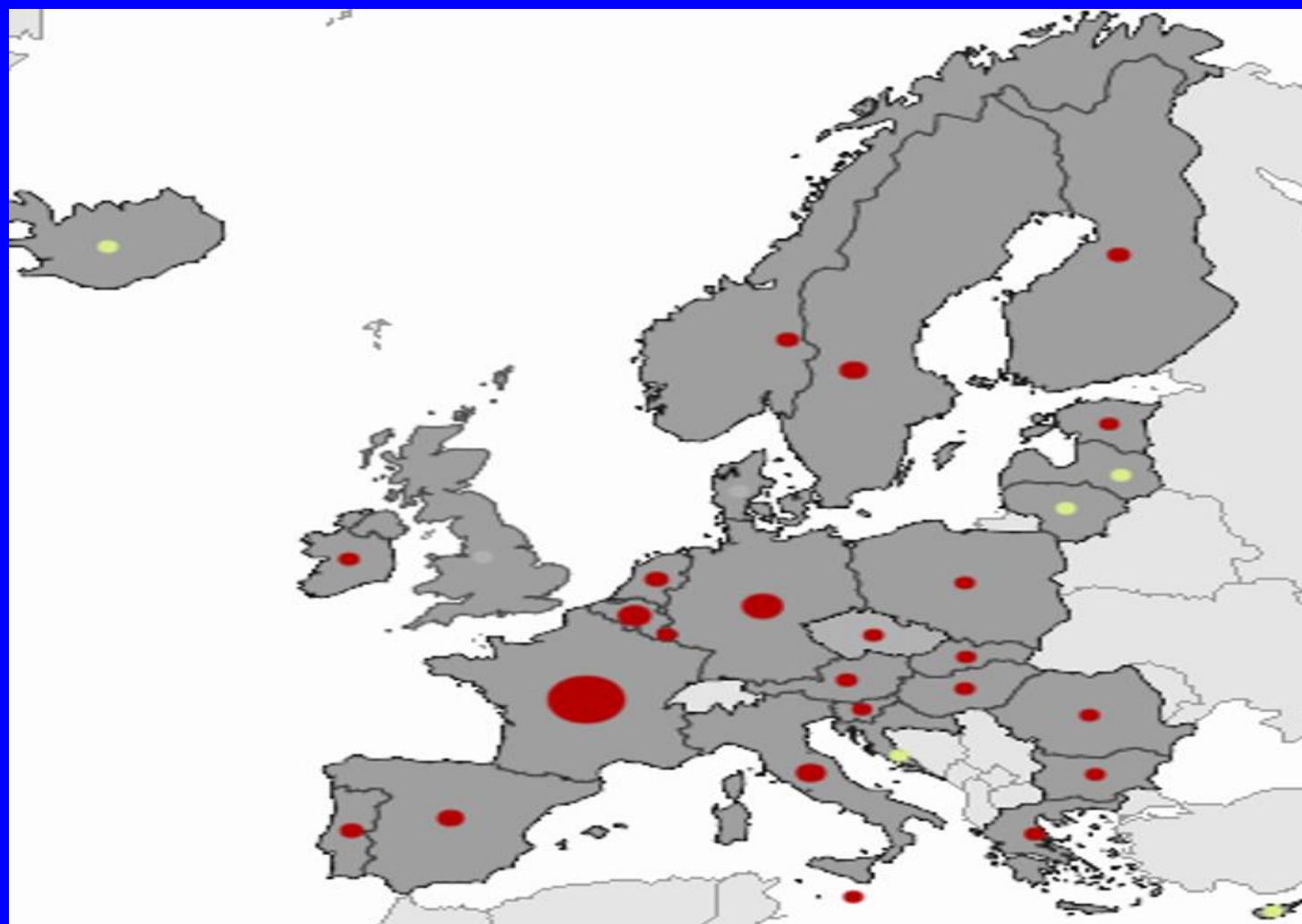
Distribution by Plasmodium species

(ECDC Surveillance Report for 2019)



MALARIA IN EUROPE, ATLAS ECDC, 2020

2.369 EU/EEA EU 2.321



Transmission modes of malaria in Europe

- Introduced malaria (mainly travel related)
- Induced malaria: the transmission results from the introduction of the parasite into a person by artificial means, usually of iatrogenic origin, including :
 - Blood transfusion
 - Organ transplant
- Airport malaria or suitcase malaria
- Shared use of needles or syringes contaminated with blood
- Congenital transmission before or during delivery

Transfusion Transmitted Malaria (TTM)

- TTM is an accidental *P.* infection caused by whole blood or a blood component transfusion from a malaria infected donor to a recipient
 - The implicated donors are semi-immune asymptomatic carriers with very low parasite load
 - Experimental evidence suggests that as few as **10 infected RBCs** can be sufficient to transmit the infection
 - *P. falciparum*, *vivax* and *malariae* are the species most frequently detected in TTM
- In this route of transmission
- *P.falciparum* persists for 1 year before being cleared,
 - *P. vivax* for 3 years
 - *P.malariae* remains as a chronic infection at low density for decades
- The mean incubation period for TTM is longer than in Mosquito- transmitted malaria(MTM)

Transfusion Transmitted Malaria

- Measures for blood safety against Malaria:
 - ✓ pre-donation questionnaire and criteria for haemovigilance for the screening of potentially infected donors
 - ✓ antibody testing on donors at risk are applied in EU based on Directive 2004/33/EC and the EDQM “Guide to the preparation, use and quality assurance of blood components” adapted in national guidelines.
 - ✓ PCR testing can also be applied if available
- Measures for organ transplantation against malaria are also defined in the EU Directive 2006/17/EC and the technical guide to the quality and safety of organs for transplantation
 - Limitations in existing diagnostic tools
- *The sensitivity and specificity of the screening strategy of blood donors remains a crucial issue in malaria as serological tests currently used do not indicate parasitaemia because antibody levels can remain elevated for many years after infection with P. falciparum and P. vivax*

In this context, new technologies to selectively inactivate pathogens without damaging cells may well represent another means of control to reduce the risk of TTM

Transfusion Transmitted Malaria

- Data from non -endemic areas
 - 100 TTM cases**
 - 45% p. Falciparum
 - 30% P. Malariae
 - 16% P. vivax
 - 4% P. ovale
 - 2% P. Knowlesi
 - 1% mixed P. falciparum/P. malariae
- **Fatal outcomes** (11/45) caused by P. falciparum
 - (2/30) by P. malariae
 - (1/4) P. Ovale

Greece 2009-2021

Malaria surveillance data

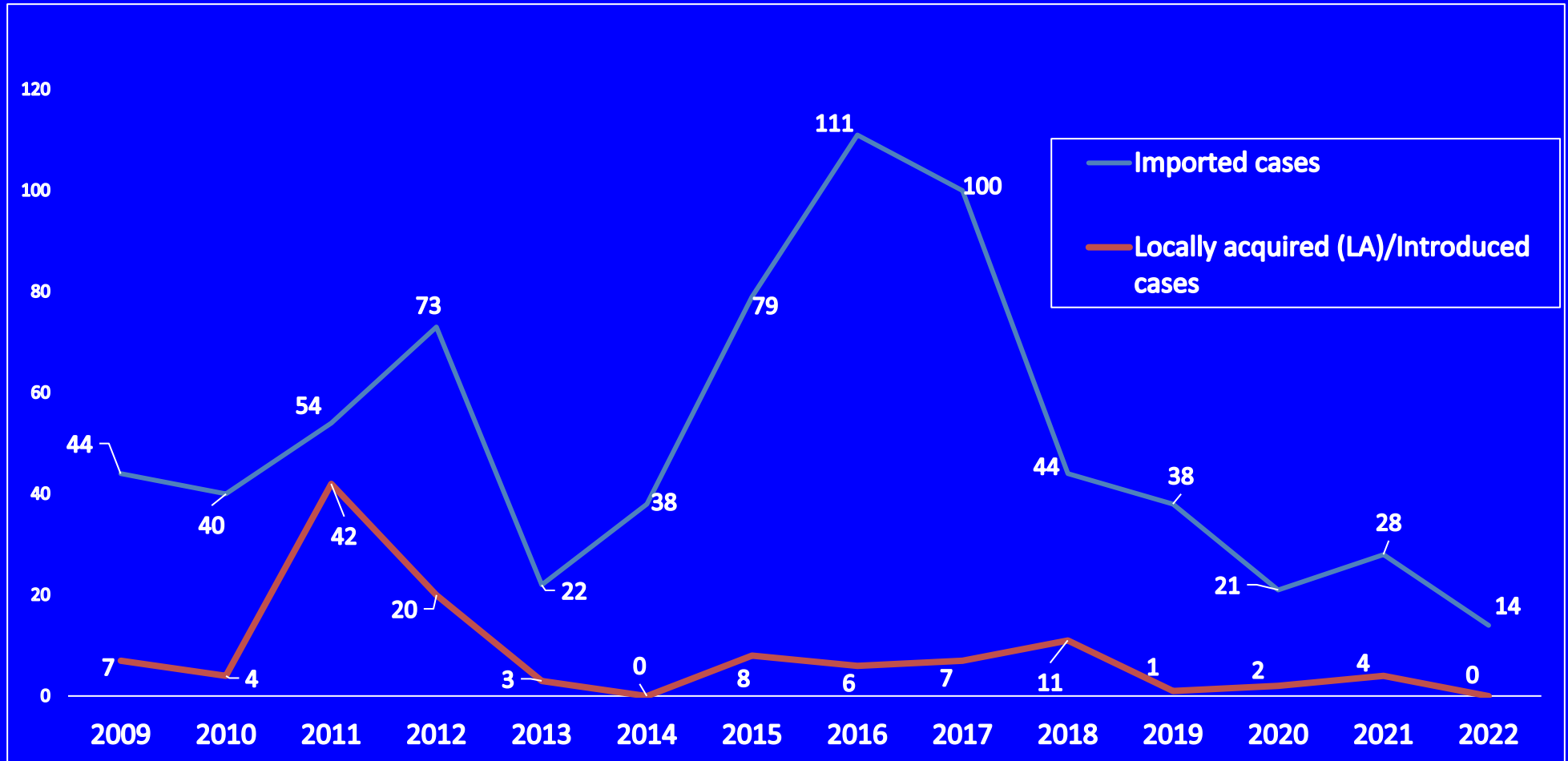
- Malaria was eliminated from Greece in 1974, following an intense control program (1946-1960)
- Since then and up to 2021, several (20-110 cases) imported cases were reported annually to the NPHO referring to patients infected abroad (returning travelers or migrants from malaria endemic countries)
- Increasing numbers of imported malaria cases are expected due to the increase of travels and population movements worldwide, a phenomenon that is observed in all developed countries

Haemovigilance before 2007

- 3 cases of TTM *P. malariae* were diagnosed in patients with surgery, lymphoma and gastrointestinal bleeding
- In the first case, the implicated donor was a 52 years old woman born in a previously endemic area. She had fever of unknown origin in 1945. A high malarial antibody titre of 1/160 was detected. The interval between acquisition of the infection and TTM was about 48 years
- Traceability studies were not possible in the other 2 cases

Greece 2009 -2022

A table of 821 reported malaria cases by year of symptom onset (for imported cases) or infection (for locally acquired cases)



Selective blood donation screening for evidence of malaria in affected areas, Greece, 2009-2019

Year	RT-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
2018 **	108	4025	4133	Negative
Total	1898	4247	6145	Negative

* In Lakonia

** In various affected
areas

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-3 α (Pvmsp-3 α), highly polymorphic
- Microsatellite markers (MS) also applied in *P. vivax* genetic diversity studies, increasing analysis of results

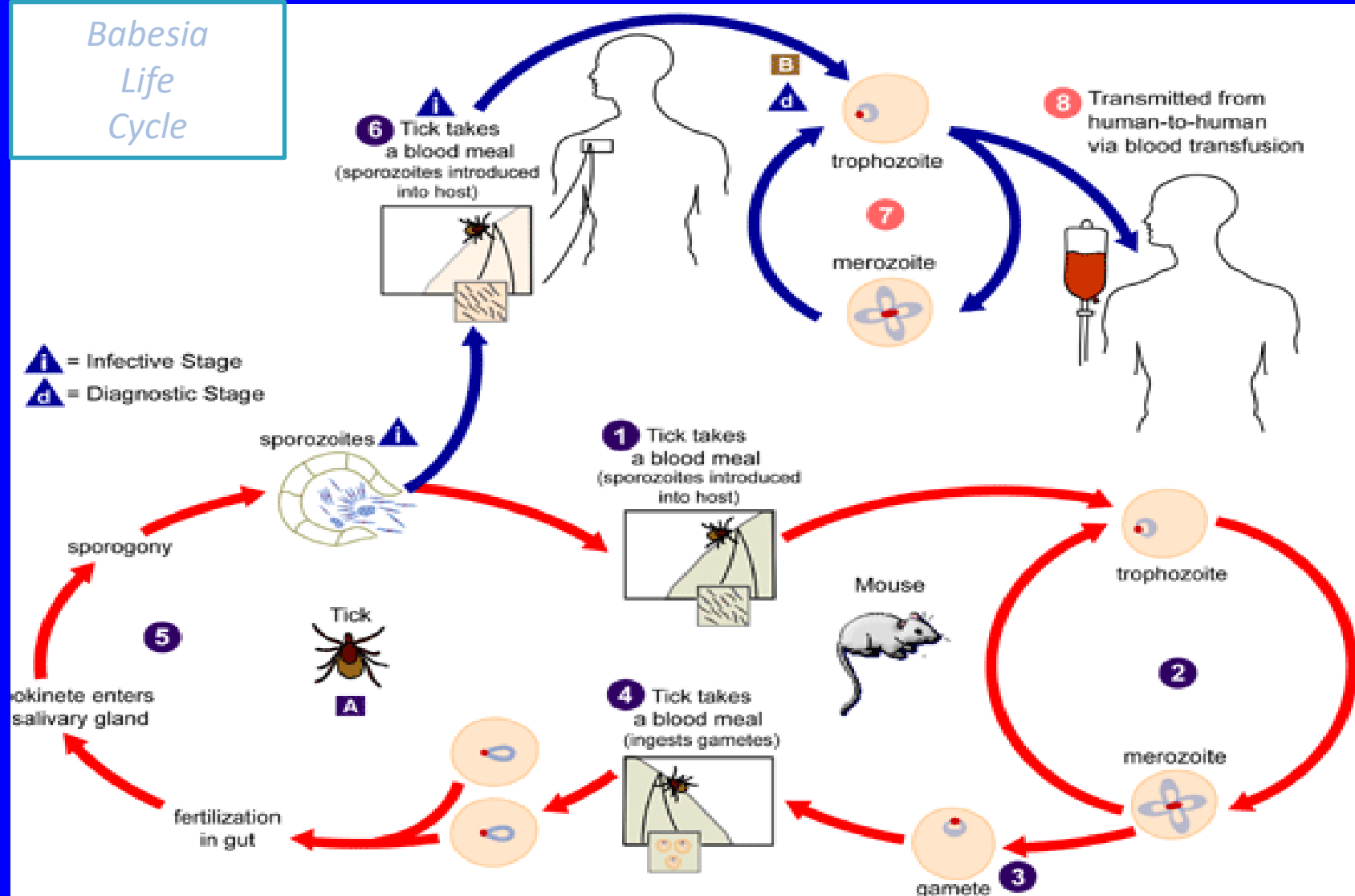
Conclusions

- Malaria is one of the world's major **Public Health problems**
- Migration, travel and climate change are risk factors for the introduction of Malaria in **Europe**, so the vast majority of malaria cases are imported and **travel-related**
- A small number of sporadic **autochthonous malaria** cases were reported in 2019 in the EU/EEA, but no sustained transmission has been reported
- **TTM risk** needs to be taken into account in order to enhance the safety of the blood supply from donors to recipients by means of appropriate screening strategies and advanced diagnostic tools:

Pathogen Reduction/Inactivation technologies may well represent another layer of control to reduce the risk of TTM and other blood-borne diseases

Babesia

Babesia Life Cycle



Background |



Nymphal tick (above) is approximately the size of a poppy seed

- **Human Babesiosis** is a worldwide emerging protozoan disease caused by several species of intraerythrocytic protozoa that are transmitted primarily by ticks including *Ixodes ricinus* (vector of babesiosis) but also through blood transfusion from an infected donor, as well as by congenital transmission from an infected mother to her baby during pregnancy or delivery, and by organ transplantation
- The main reservoirs of this parasite are cattle, roe deer and rodents
- Babesia infects and destroys RBCs. **Most infections seem to remain asymptomatic.** For clinical cases, the incubation period varies between one to eight weeks but delayed appearance of symptoms after a prolonged asymptomatic infection may occur after several months

Background II – Clinical features

- Babesiosis In humans varies from mild to severe and lethal
- Beginning with non-specific flu-like symptoms, the acute illness generally presents with **intravascular haemolysis** causing haemoglobinuria, jaundice, non-periodic fever, headaches, chills and myalgia
- This may last from several days to a few months
Shock-like syndrome with renal failure and pulmonary oedema can occur and may be fatal

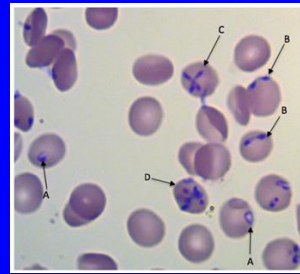
Criteria associated with high morbidity and mortality

- Parasitaemia > 10%
- Haemoglobin level < 10gr/dl
- Previous splenectomy
- Adult respiratory distress syndrome
- Acute renal failure

Background III - Treatment

- Treatment of human babesiosis in Europe is based on clindamycine and quinine, associated with blood exchange transfusion.
- Clindamycine may sometimes be used alone and in mild cases exchange transfusion can be avoided.
- Atovaqione associated with azithromycin is also effective
- No vaccination is currently available

Babesiosis in Europe



- The first case of human Babesiosis in Europe was described in 1956 in the former Yugoslavia, now Croatia in a 33year-old tailor and part-time - farmer who had been splenectomised following a traffic accident 11 years earlier .

The patient presented with fever and severe haemoglobinuria eight days after feeling unwell and died two days later. The parasites detected in blood smears were identified as Babesia Bovis, a species with characteristics of Babesia Divergens

- Up to the end of 2021 about 60 cases of different species of human B. have been reported in Europe
- *Although the disease is rare, it is significant because the majority of cases present as life - fulminant infection mainly in splenectomised and immunocompromised patients*
- *Most European forms are distinct entities, concerning epidemiology ,human susceptibility and clinical management*

B.Bovis, B.Divergens, B.Venatorum and and European B.Microti

Babesiosis in Europe

Overall 51 autochthonous cases have been identified
in 19 countries

Year	Parasite	n cases	Clinical course/Outcome	
1957-2021	<i>B.divergens</i>	35 cases	mild- lethal	} 12 Deaths
2003-2017	<i>B.venatorum</i>	5 cases	moderate to severe	
2014-2021	<i>B.microti</i>	11 cases	moderate to severe	

Another 13 cases were imported into Europe

Comment

Serological studies suggest that despite the rarity of recognised Babesia cases in Europe, these infections may be rather common

The European *Babesia microti*

- Human *B.microti* infections is considered to be a species complex, mainly infecting small mammals
- Human *B.microti* infections have expanded across the northeast coast of USA in recent decades and several cases in Europe have been associated with travel from USA
- In contrast, very few autochthonous cases have occurred in Europe. The first authenticated in Germany caused a moderate illness in a spleen-intact but immunocompromised patient
- A few mild or asymptomatic other cases have since been recorded, but it is clear that the *B.microti* strains present in Europe, where it is common in rodents and ticks, are not as infectious or pathogenic to humans as those in the USA where *B.microti* infections give rise to approximately 2000 cases annually

Transfusion –Transmitted Babesiosis (TTB)

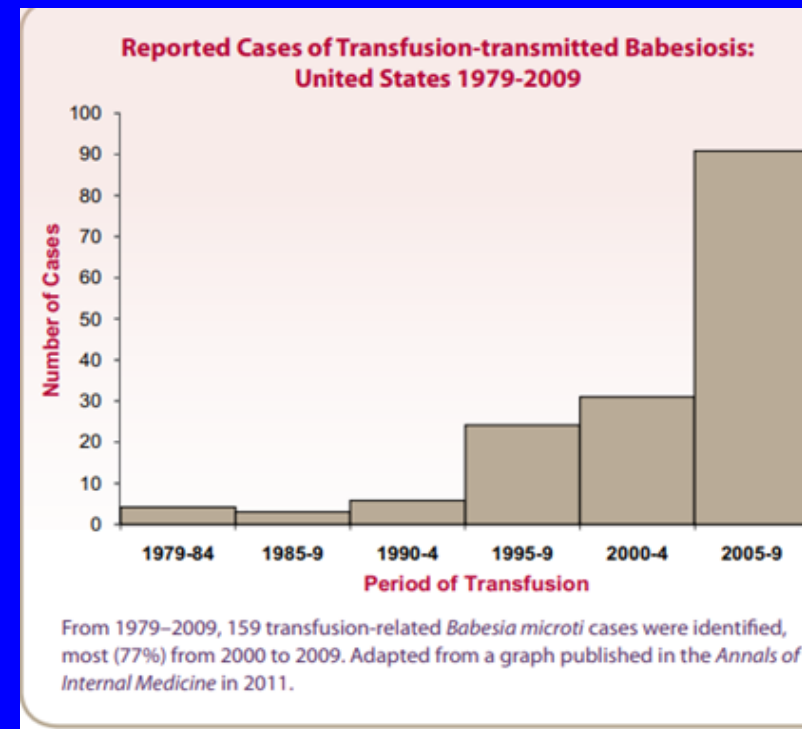
- TTB was first recognised in 1979, ten years after the first tick-transmitted case was described. The causative agent was *Babesia microti*, the most common cause of human Babesiosis and TTB
- TTB can be a severe illness with a mortality rate of about 20%. It is most commonly acquired by neonates, immunocompromised patients and those with sickle cell anaemia and thalassaemia, organ transplantation and splenectomy
- *B. microti* infection has recently been determined to be the most common transfusion-transmitted pathogen in the northeastern and northern midwestern USA
- A second species involved in TTB is *B. duncani*, but only a few cases have been described
- Babesiosis is difficult to identify in blood donors because about a quarter of adults experience asymptomatic *B. microti* infection

Prevention of TTB Microti : the American experience

- Given that TTB imposes a significant health burden on the US population, and that the number of cases is increasing with varying distribution even in the same regions, **donor deferral and optimal screening strategies** to prevent TTB using :
 - *B. microti* antibody (e.g. IFA) and /or PCR assays
relying on amplification of 18rRNA sequencesare still in focus under a **cost - effective** screening programme of the FDA to prevent TTB with the criterion of not exceeding the target threshold cost that is used for interventions mitigating other infectious risks of transfusion

Blood donor deferral and re-entry strategies: the American model

- The current standard is :
 - **exclusion of potential donors** with history of babesiosis or laboratory evidence of previous infection
 - **rescreen donors** a year after they have tested positive and allow re-entry to the donor pool if repeat antibody and PCR screening results are negative
 - In Europe, permanent deferral criteria for donors include babesiosis (Directive 2004/33/EC)



Babesia divergens and *Babesia venatorum*

- The second case was a fatal *B.divergens*, in 1967 in a splenectomised man who contracted the infection on holiday in the west of Ireland
- Further cases followed in UK and France.
- To date, cases have been reported in at least 19 European countries, almost always fulminant in splenectomised patients and attributed to *B.divergens*
- A second zoonotic species emerged in 2003 in Italy and Austria named *B.venatorum* , all in splenectomised patients who survived, thus indicating a milder course of infection than that of *B.divergens*, although treatment has improved markedly since the appearance of zoonotic babesiosis

Key areas of uncertainty

- Many biological and epidemiological data on human pathogenic *Babesia* species are lacking :
 - the formal characterisation of the identity of B. species and genotypes involved in each human case as well as better characterisation of the epidemiology of the infection in animal reservoirs and vectors
 - development of accurate diagnosis for the management of human risk
- (rapid diagnosis in clinical cases, control of the risk of transfusional transmission in splenectomised or immunocompromised patients)

ECDC 2022 ,Facts about babesiosis

Recent findings on the occurrence and incidence of Babesiosis in humans and animals

Affected Areas

- **Southeastern Europe** : Bosnia and Herzegovina, Croatia, Serbia
- **Central Europe** : Austria, Czech Republic, Germany, Hungary, Lux, Poland, Slovakia, Swiss
- **Northern and Northeastern Europe** : Lithuania, Latvia, Estonia, Iceland, Denmark, Finland, Sweden and Norway

Recorded cases of human B. and selected species of domesticated animals are still rare, but their numbers is expected to rise in the coming years

This is because of the widespread and longer seasonal activities of Ixodes Ricinus as a result of climate change and because of the more extensive use of better molecular diagnostic methods

- Bovine Bovis has a re-emerging potential because of the likely loss of herd immunity
- Canine Bovis is rapidly expanding in central and northeastern Europe, its occurrence correlating with the rapid, successful analysis of the ornate dog tick in Europe

- **In Greece** serological and PCR studies in dogs, sheep, cattle and rodents in Lesvos, Central and Eastern Macedonia showed presence of B. divergens. High endemics of pathogens Anaplasma spp (A- phagocytophilum, A. ovis, A. carpa in sheep)

No human B. case has been reported up to now

Diagnostic limitations in European Babesiosis

- *Babesia* Sp. Infection can be assessed by microscopic examination of stained blood smears
- Serology does not allow species identification but used in epidemiological studies it can assist in evaluating exposure to *Babesia* Spp
- *B. microti* can be distinguished serologically from *B. divergens* and *B. venatorum*, but the latter two are antigenically similar
- DNA sequence discrimination is not only relatively swift, but can also be used to identify *Babesia* species and it is now the method of choice for determining parasite identity
 - The 18SrRNA gene is by far the most commonly used locus for *Babesia* identification

Conclusions

- The spread of infectious diseases among people and animals is a worldwide challenge
- Climate change, migration and travel are some of the main contributing factors for this development
- In Europe and elsewhere, zoonoses such as human Babesiosis are spreading and threaten Public Health and the Blood Supply, organ transplantation and congenital transmission of these infections in pregnancy and delivery
- Advances in laboratory methods are required to increase our knowledge and understanding of the diversity of zoonotic *Babesia* species and the role that domestic animals, wildlife and tick population play in their maintenance
- Further development of laboratory tools including Pathogen Inactivation for the protection of the blood supply will assist in significant donor retention and likely increased blood availability
- The situation is of major concern and it is recommended more extensive and frequent standardized monitoring by using a “ONE HEALTH APPROACH”

- MDPI Microorganisms 2022, 10, 945 Anna Bajer et al

Thank you
Any questions?