SoHO-Net Meeting: Organs group

18 – 19 June 2024, Stockholm

Session 1
Introduction and presentations
18 June

Session overview

1. **Director's welcome** – Pamela Rendi-Wagner, ECDC
2. **Introduction** – Marieke van der Werf, ECDC
3. **Key objectives for the meeting** – Jenny Mohseni Skoglund, ECDC
4. **Presentations network members and invited experts** – *Tour de table*

Welcome and introduction

Pamela Rendi-Wagner, ECDC

Welcome and introduction

Marieke van der Werf, ECDC

ECDC mission & role

To identify, assess and communicate current and emerging threats to human health posed by infectious diseases.

Disease Surveillance & Epidemic intelligence

Response support & Risk assessments

Preparedness & capacity strengthening

Scientific advice & guidance

EU and external stakeholders & Country support

Public health training

Communication

Vaccine-preventable diseases and Immunisation

Sexually transmitted infections, Blood-Borne Viruses and Tuberculosis

ECDC SoHO team

Antimicrobial resistance and healthcare-associated infections

Emerging, Food and vector-borne diseases

Sexually transmitted infections, blood-borne viruses and tuberculosis section

SDG-targeted diseases group

- Hepatitis B and C
- HIV
- Sexually transmitted infections
  - Chlamydia
  - Gonorrhoea
  - Syphilis
- Tuberculosis

SoHO team


Veronica Cristea

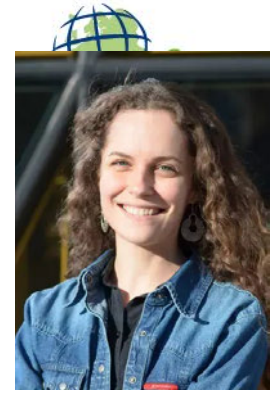

Charlotte Deogan


Els Driessens


Erika Duffell


Marijana Kukolj


Csaba Ködmön


Ana Finatto-Canabarro

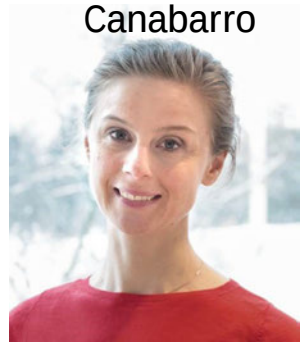

Francois-Xavier Lamy

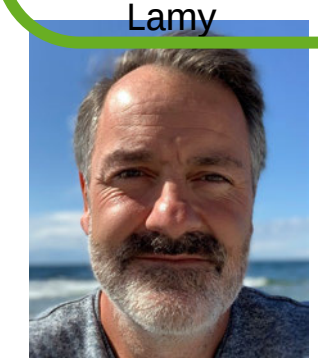

Flavia Cunha

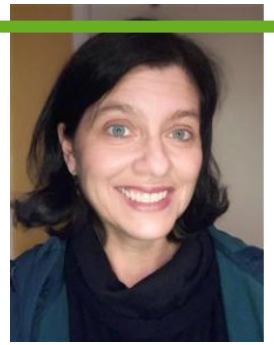

Jenny Mosheni Skoglund


Otilia Mårdh


Ndeindo Ngangro


Lina Nerlander


Teymur Noori


Anastasia Pharris


Juliana Reyes


Senia Rosales-Klintz


Janelle Sandberg


Marieke van der Werf

EU regulations relevant for SoHO

- Regulation (EC) No 851/2004 of the European Parliament and of the Council of 21 April 2004 establishing a European Centre for Disease Prevention and Control
- Regulation (EU) 2022/2370 of the European Parliament and the Council of 23 November 2022 amending Regulation (EC) No 851/2004 establishing a European Centre for Disease Prevention and Control
- Regulation (EU) 2022/2371 of the European Parliament and the Council of 23 November 2022 amending Regulation (EC) of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU
- Directive 2010/45/EU of the European Parliament and of the Council of 7 July 2010 on standards of quality and safety of human organs intended for transplantation
- Proposal for a Regulation on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC

Framework for ECDC support to EU/EEA countries and the European Commission to reach microbial safety of substances of human origin

Prevention of communicable disease transmission through application of substances of human origin

Coordinate SoHO network	Provide guidance on microbial safety	Threat detection, assessment, and response

Source: https://www.ecdc.europa.eu/en/publications-data/ecdc-framework-relating-substances-human-origin-soho

Coordinate SoHO network

- Network of Member State services supporting the use of substances of human origin (SoHO-Net). Four sub-networks with National Focal Points and observers:
  - Blood
  - Tissues and cells
  - Organs
  - Medically assisted reproduction
- SoHO Network Coordination Committee with elected members from the network
- Regular meetings of the SoHO Network Coordination Committee and of the four SoHO sub-networks
- EpiPulse platform for information exchange and collaboration between countries

Provide guidance on microbial safety

- Develop and update guidelines as referred to in the SoHO Regulation
  - Guideline development process according to ECDC procedures for developing guidelines
  - Collaboration with the European Directorate for the Quality of Medicines & HealthCare (EDQM) to ensure that technical guidelines published by EDQM and ECDC are aligned
- Develop guidance and recommendations on topics relevant to the microbial safety of SoHO at the request of the SoHO network, the European Commission or on own initiative

Threat detection, assessment, and response: Monitor threats and outbreaks

Detect, monitor, and report on serious cross-border threats to health related to SoHO.

- Results of daily screening of various information sources
- Reports of cases of infectious diseases and pathogens that may threaten microbial safety of SoHO in the EU/EEA in EpiPulse
- Monitoring of serious adverse reactions*

→ Discussion of identified threats and an initial assessment of appropriate ECDC actions.

* Serious adverse reaction (SAR) is defined in the Proposal for a Regulation as an adverse reaction that results in death, a life-threatening, disabling or incapacitating condition, including transmission of a pathogen, hospitalisation or prolongation of hospitalisation, or the need for a major clinical intervention to prevent or reduce the effects.

Threat detection, assessment, and response: Perform risk assessments and launch alerts

- Provide risk assessments including science-based recommendations and options for response in the case of a serious cross-border threat to health
- Launch an alert in the EU SoHO Platform when the risk assessment indicates a new risk to the safety of SoHOs
- Support response coordination in the Health Security Committee

Threat detection, assessment, and response: Provide advice on serious adverse reactions*

SoHO National Authority will inform ECDC of serious adverse reactions concerning a transmission of a communicable disease that is rare, or unexpected for that SoHO type.

ECDC will support relevant follow-up actions including providing advice or information to SoHO National Authorities on options for response.

* Serious adverse reaction (SAR) is defined in the Proposal for a Regulation as an adverse reaction that results in death, a life-threatening, disabling or incapacitating condition, including transmission of a pathogen, hospitalisation or prolongation of hospitalisation, or the need for a major clinical intervention to prevent or reduce the effects.

Empowering EU/EEA countries, the EC and other partners to drive public health policy and practice

Through the building blocks detailed in this framework, ECDC aims to achieve the following:

- Robust SoHO network and mechanisms for the exchange of information.
- Guidelines available and updated as needed for the prevention of donor-derived communicable disease transmission through the application of SoHO.
- Well-functioning system for identification and information sharing of serious adverse reactions and communicable disease outbreaks relevant to the microbial safety of SoHO.
- High-quality risk assessments with science-based recommendations and options for response and timely alerts when a new risk to the safety of SoHOs is identified.

Aim and key objectives for the meeting

- To get to know each other and understand the network and the role of the NFPs
- To update the SoHO-Net Organs group and invited participants on ECDC scientific outputs and activities related to donor derived communicable diseases transmission
- To discuss current challenges in the fields related to donor derived communicable diseases transmission
- To exchange good practice of donor testing strategies
- To share experiences of reporting serios adverse reactions and events
- To identify and prioritize main topics for activities for the SoHO-Net Organs group.

Session 2
SoHO-Net Organs group
18 June

Session overview

1. **The role of ECDC networks and the SoHO-Net Organs group** – Jenny, Mohseni Skoglund, ECDC
2. **Questions and answers** – All
3. **Breakout session:** topics and expectations for the role of ECDC in the field of SoHO safety for organs

ECDC networks

Jenny Mohsenis Skoglund, ECDC

Dedicated Networks

*"The Centre shall **promote and coordinate the networking of bodies, organisations and experts** operating in the Union in the fields relevant to the Centre's mission, including networks arising from public health activities supported by the Commission, and operate dedicated networks on surveillance, while ensuring full compliance with rules on transparency and conflicts of interest."*

Dedicated network means any specific network on diseases, related special health issues or public health functions that is supported and coordinated by the Centre and is intended to ensure collaboration between the coordinating competent bodies of the Member States.

Disease and Laboratory Networks

and networks dedicated to health issues*

Antimicrobial resistance and healthcare-associated infections

- European Antimicrobial Resistance Surveillance Network (EARS-Net)
- European Surveillance of Antimicrobial Consumption Network (ESAC-Net)*
- Healthcare-associated Infections Surveillance Network (HAI-Net)*
- European Antimicrobial Resistance Genes Surveillance Network (EURGen-Net)

Emerging and vector-borne diseases

- Emerging and Vector-borne Diseases Network (EVD)
- Emerging Viral Disease-Expert Laboratory Network (EVD LabNet)
- European Network for sharing data on the geographic distribution of arthropod vector, transmitting human and animal disease agents (Vector-Net)*

Food- and waterborne diseases, zoonoses

- European Food- and Waterborne Diseases and Zoonoses Network (FWD-Net)
- European Legionnaires' disease Surveillance Network (ELDSNet)
- European Creutzfeldt-Jakob Disease Surveillance Network (EuroCJD)

Respiratory tract infections

- European Tuberculosis Surveillance Network
- European Reference Laboratory Network for TB (ERLTB-Net)
- European Influenza Surveillance Network (EISN)
- European Reference Laboratory Network for Human Influenza (ERLI-Net)
- European COVID-19 Surveillance Network (ECOVID-Net)
- European COVID-19 reference laboratory network (ECOVID-LabNet)

HIV, STI and blood-borne viruses

- European Sexually Transmitted Infections Network
- European Gonococcal Antimicrobial Surveillance Programme (Euro-GASP)
- European Network for HIV/AIDS
- European Network for hepatitis B and C surveillance

Vaccine-preventable diseases and invasive bacterial infections

- European Invasive Bacterial Diseases Surveillance Network (EU-IBD)
- EU laboratory Network for surveillance of Pertussis (EUPertNet)
- European Diphtheria Surveillance Network (EDSN)
- Network on measles, mumps, rubella surveillance (MMR)

Network for the Microbiological Safety of Substance of Human Origin (SoHO)*

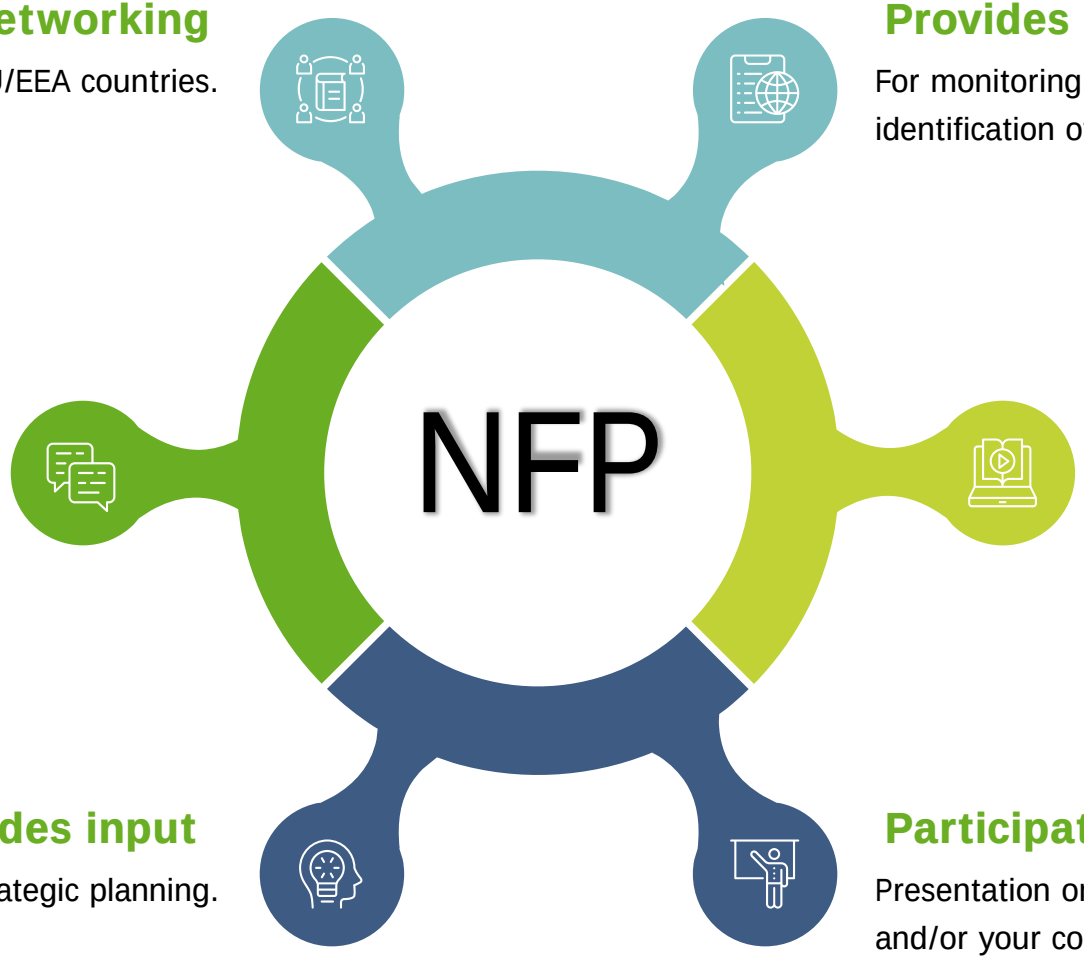
What?

Networking

Interacting with other EU/EEA countries.

Provides information

For monitoring the situation in your country and for identification of country needs.



Coordinates

Interactions with national stakeholders.

Provides technical advice

Review/comment technical documents .

Provides input

To ECDC strategic planning.

Participates in ECDC activities

Presentation on your subject area and/or your country.

How?

E-mail exchange

- Requesting information from your country.
- Requesting information to ECDC.

Targeted request

- Surveys or external consultations.
- Country visits.

Bilateral interactions

- With other EU/EEA countries.
- Study visits/expert exchanges.

ECDC information systems

- Discussion forums in EpiPulse.

Video conference

- Ad hoc or regular virtual meetings.

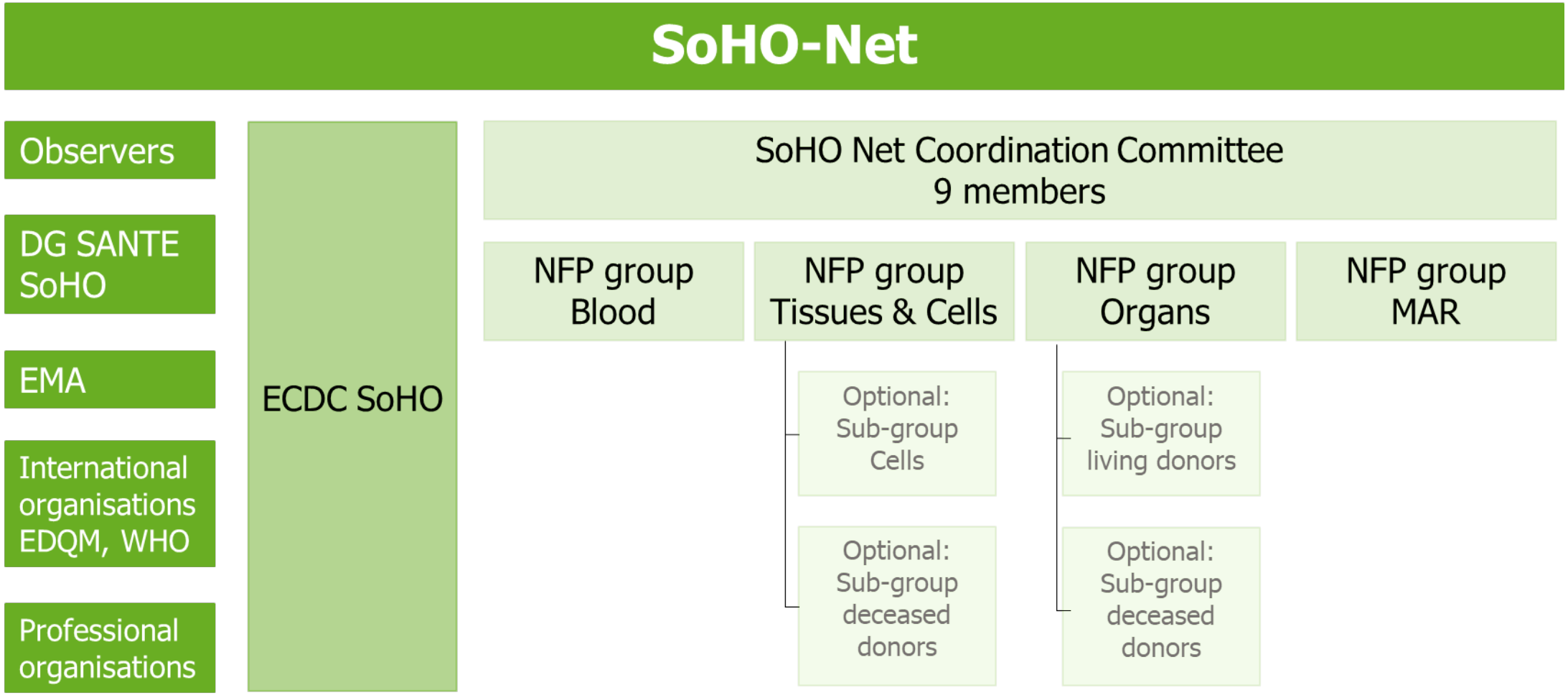
The SoHO network

Regulation of the European parliament and of the Council amending Regulation (EC) No 851/2004 establishing a European Centre for disease prevention and control

http://data.europa.eu/eli/reg/2022/2370/oj

brings a **legal framework** for ECDC's recommendations to Member States regarding health threats preparedness, and also **for hosting expert networks**.

ECDC SoHO network (SoHO-Net)



Main objectives of the SoHO-Net

- Encourage cooperation between Member States
- Help to ensure that SoHO are microbially safe by monitoring, assessing and helping to address relevant disease outbreaks that can pose cross-border threats to health
- Support the detection, monitoring and reporting on serious cross-border threats to health related to SoHO
- Enhance preparedness and response planning activities in the Union
- Safeguard patients in need of SoHO

Responsibilities of the SoHO NFPs

- Cooperate closely and communicate with National Competent Authorities
- Support and advise NCA in the establishment of the national communication channels
- Support ECDC in regular monitoring of microbial safety measures
- Contribute to the assessment of the impact of scientific advice produced by ECDC
- Report to the EpiPulse and analyse cases of infectious diseases and pathogens related to SoHO that may threaten public health in the EU/EEA

The SoHO-Net Coordination Committee (NCC)

Consists of 9 members of the SoHO-Net, nominated by SoHO-Net members

- 2 members from each Blood, Organ and MAR group
- 2 + 1 members from Tissues and Cells, respectively
- Elected for a period of 3 years
- Can be re-elected
- Elected by the Network

Tasks:

- Works closely with ECDC in between the network group meetings
- Provides advice on urgent matters
- Contributes to the agenda of the regular network meetings
- Appoints a chair among its members

The SoHO-Net Coordination Committee (NCC)

Appointed by the ECDC Director

NCC members	Number of members	Elected member
NFP Blood	2	Anna Margrét Halldórsdóttir, Iceland Imad Sandid, France
NFP Human Organs	2	Sophie Lucas-Samuel, France Paolo Antonio Grossi, Italy
NFP MAR	2	Ioana Rugescu, Romania Sara Pimentel, Portugal
NFP Tissues and Cells	3	Vacant Gorazd Čebulc, Slovenia Vacant

SoHO-Net Organs group – Expectations and topics
Group discussion

Breakout session: share expectations on ECDC activities in the field of Organs and describe topics for activities for the SoHO-Net Organs group

You will be divided into 5 groups with one facilitator per group to guide you. Each group you will:

1. Share and discuss your expectations on the role of ECDC and the SoHO-Net Organs group in the field of Organs safety. E.g.,: platform to share good practices in the prevention of communicable disease transmission.

2. Propose and discuss topics for activities for the SoHO-Net Organs group. E.g.,: Need for guidance on the screening of arboviruses.

Summarize your discussion and conclusions in bullet points and nominate one or two persons who will present the summary of the discussions, orally or with slides.

After the coffee break: each group will have 5 minutes for presentation, followed by a common discussion. The proposed topics will be discussed again at the end of the meeting.

Session 3
ECDC activities and Organs safety in the context of the new SoHO regulation
18 June

Session overview

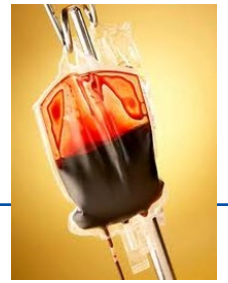
1. **Presentation of the SoHO regulation** – Stefaan Van der Spiegel, DG SANTE
2. **Presentation of ECDC technical guidelines** – Francois-Xavier Lamy, ECDC
3. **ECDC guidelines for HIV and hepatitis B and C** – Flavia Cunha, ECDC
4. **Questions and answers** – All
5. **The impact of the SoHO regulation on Organs safety – horizon scanning** – Martina Brix-Zuleger, NFP Austria
6. **Discussion on the overlap between tissue and organ donors testing and considerations in the context of the new SoHO regulation** - All

A new EU Regulation on standards of quality and safety for substances of human origin intended for human application

SoHOnet meeting organs
ECDC, Stockholm, 18 June 2024

(Slides for dissemination

Current EU legislation on safety and quality of substances of human origin



Transfusion

Medicines

Bone marrow transplant

MAR

Tissue transplantation

BLOOD & PLASMA

TISSUES & CELLS

EU legislation since 2002
(4 Directives)

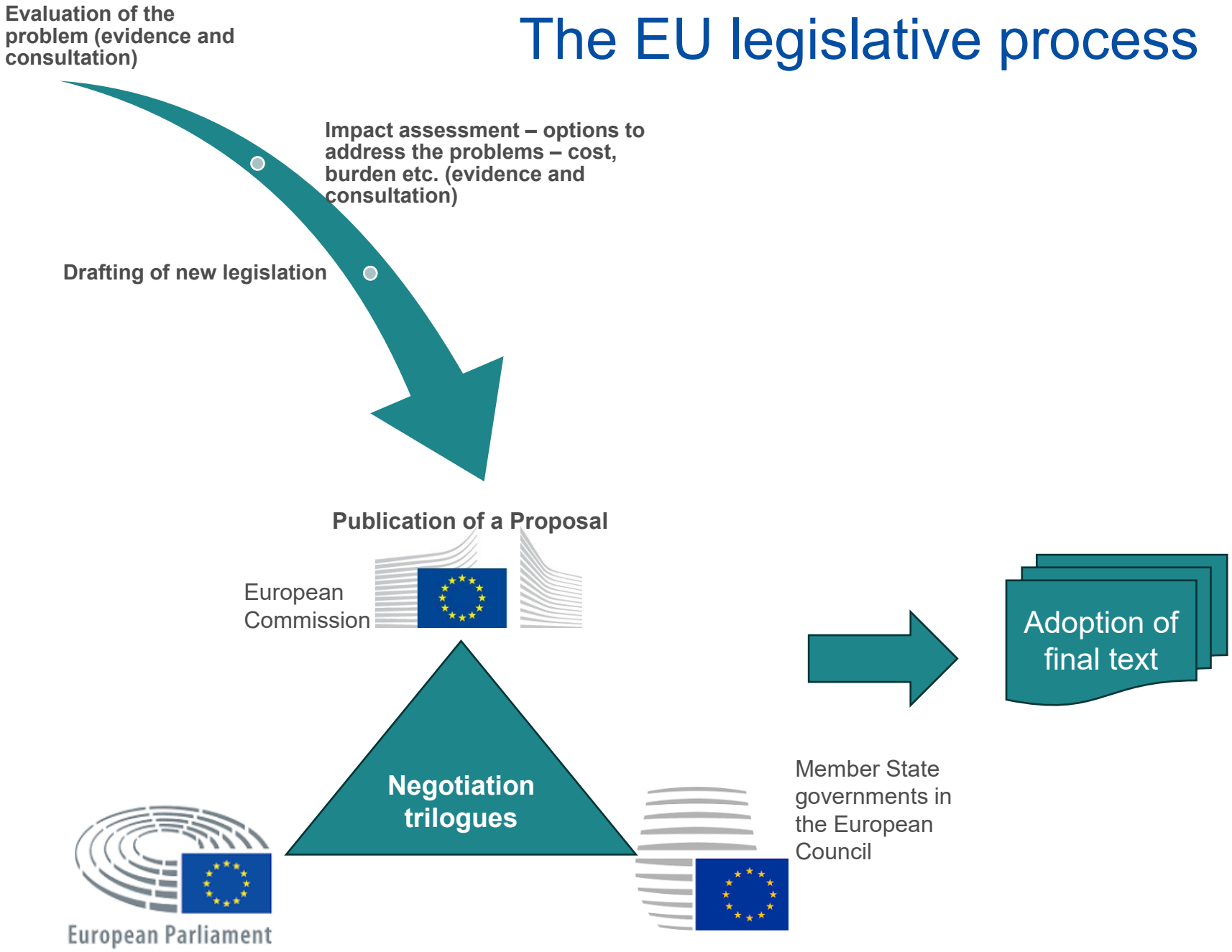
EU legislation since 2004
(4 Directives)

ORGANS

EU legislation since 2010
(2 Directives)

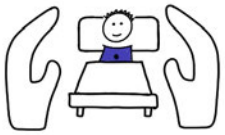
European Commission

The EU legislative process



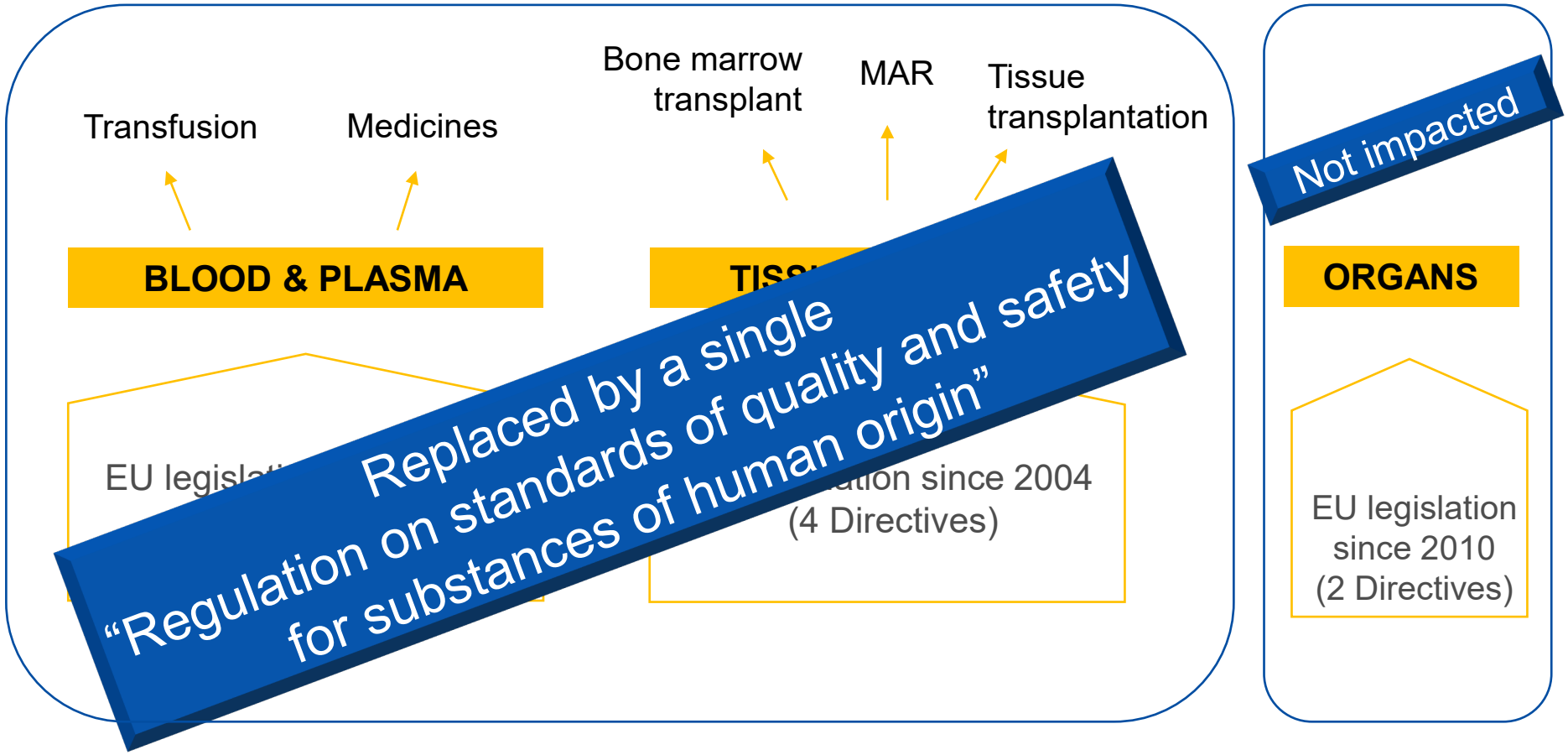
Evaluation of the Blood, Tissue and Cell legislation - published in 2019

Overall – the legislation led to increased safety and quality of BTC but gaps and shortcomings were identified

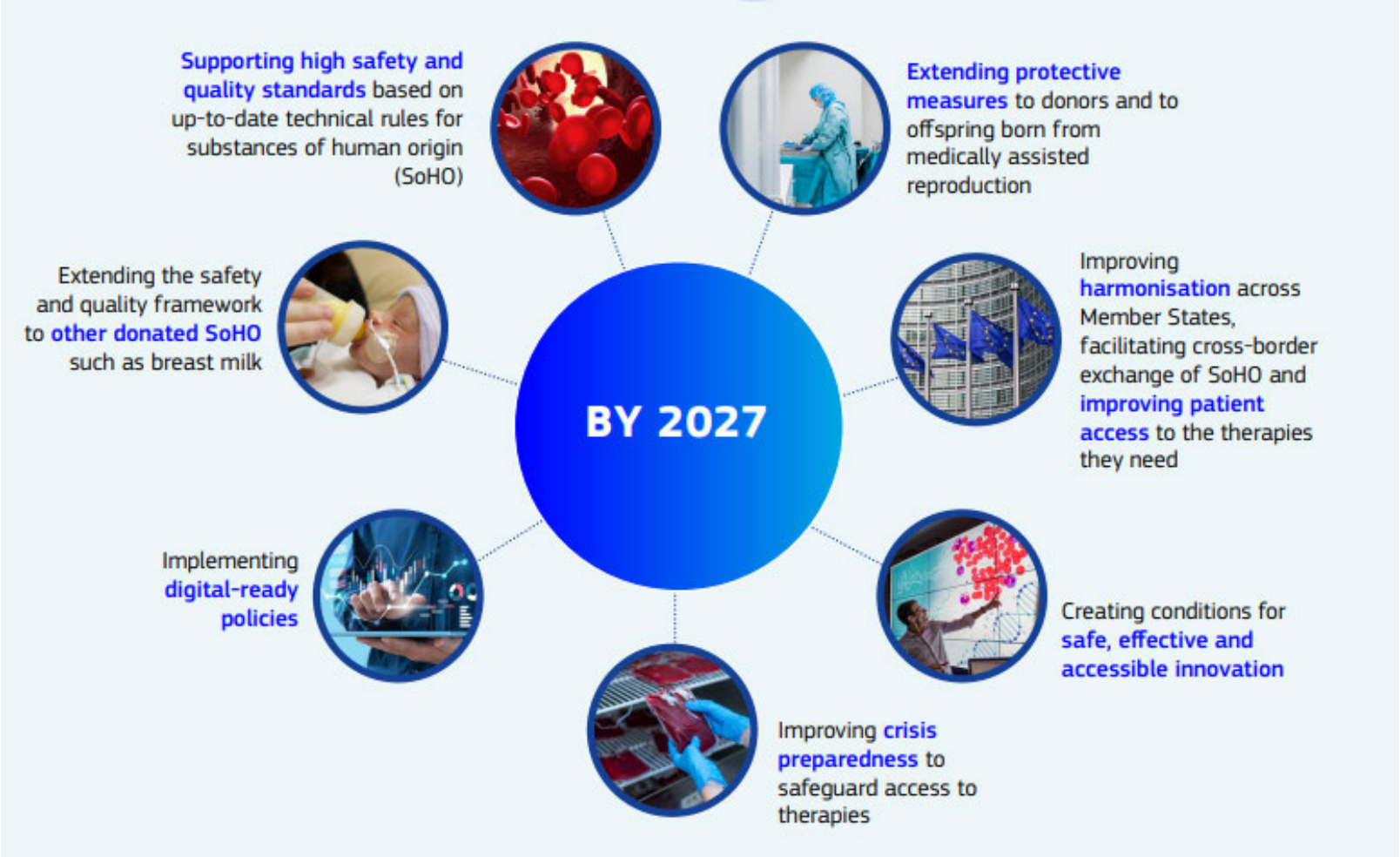
	**1. Patients are not fully protected from avoidable risks because some rules are out of date**
	**2. Legislation does not mitigate risks for BTC donors and for children born from donated eggs, sperm or embryos**
	**3. Member States have divergent approaches to oversight**
	**4. Full potential of innovative therapies is not reached for patients**
	**5. Patients are vulnerable to interruptions in EU supply of some BTC**

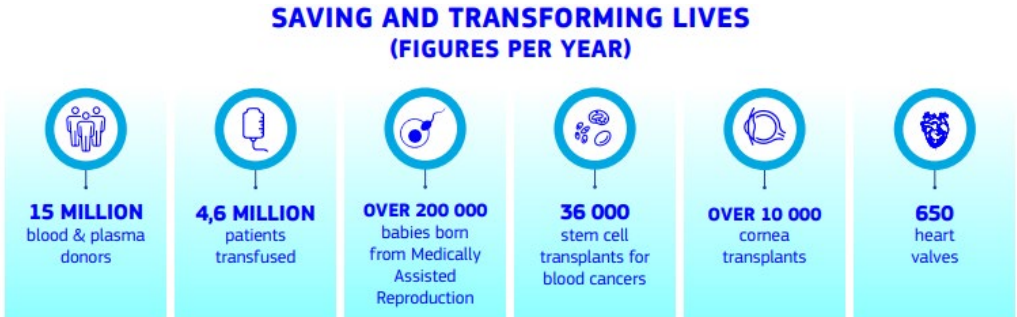
CoVID confirmed problems

Current EU SoHO legislation on safety and quality



Key improvements





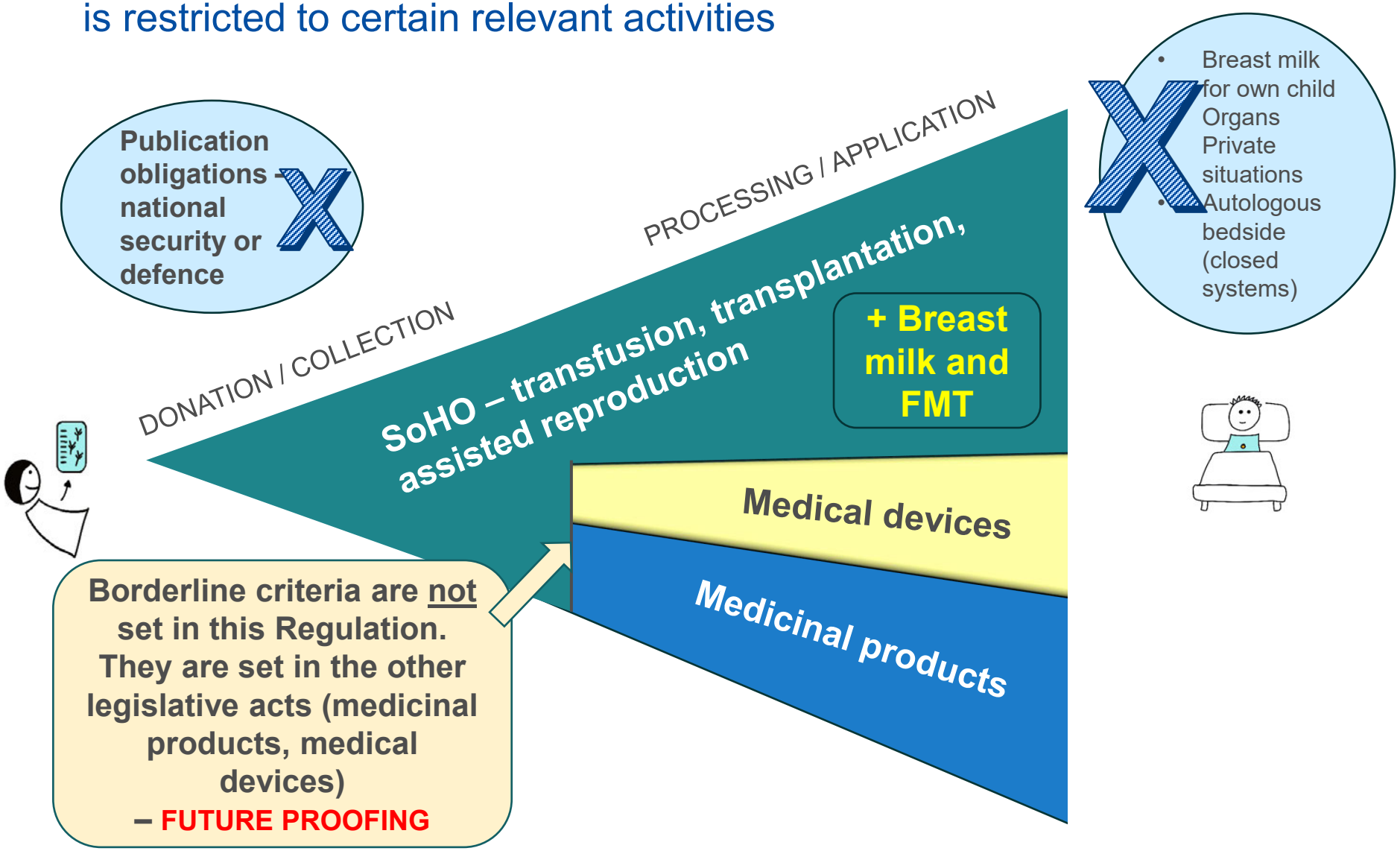
https://health.ec.europa.eu/blood-tissues-cells-and-organs/overview/proposal-regulation-substances-human-origin_en

Key new and changed concepts

- **Scope and advice**
- **SoHO activities, entities and establishments**
- **SoHO Preparations and their authorisation**
- **Standards and hierarchy of technical guidelines**
- **Donor Protection and Voluntary Unpaid Donation**
- **Recipient and offspring protection**
- **Vigilance**
- **Supply continuity**
- **Digitalisation – the SoHO platform**

This presentation explains the concepts in the Regulation, as proposed by the Commission and amended during negotiations.

Scope: Regulation covers all steps for all SoHO (some limited provisions for autologous SoHO), unless processing or application steps fall under scope of other EU frameworks – then SoHO regulation is restricted to certain relevant activities



In cases where SoHO **move to another framework** – which SoHO provisions apply? Article 2(6)

The following activities are regulated by the SoHO Regulation:

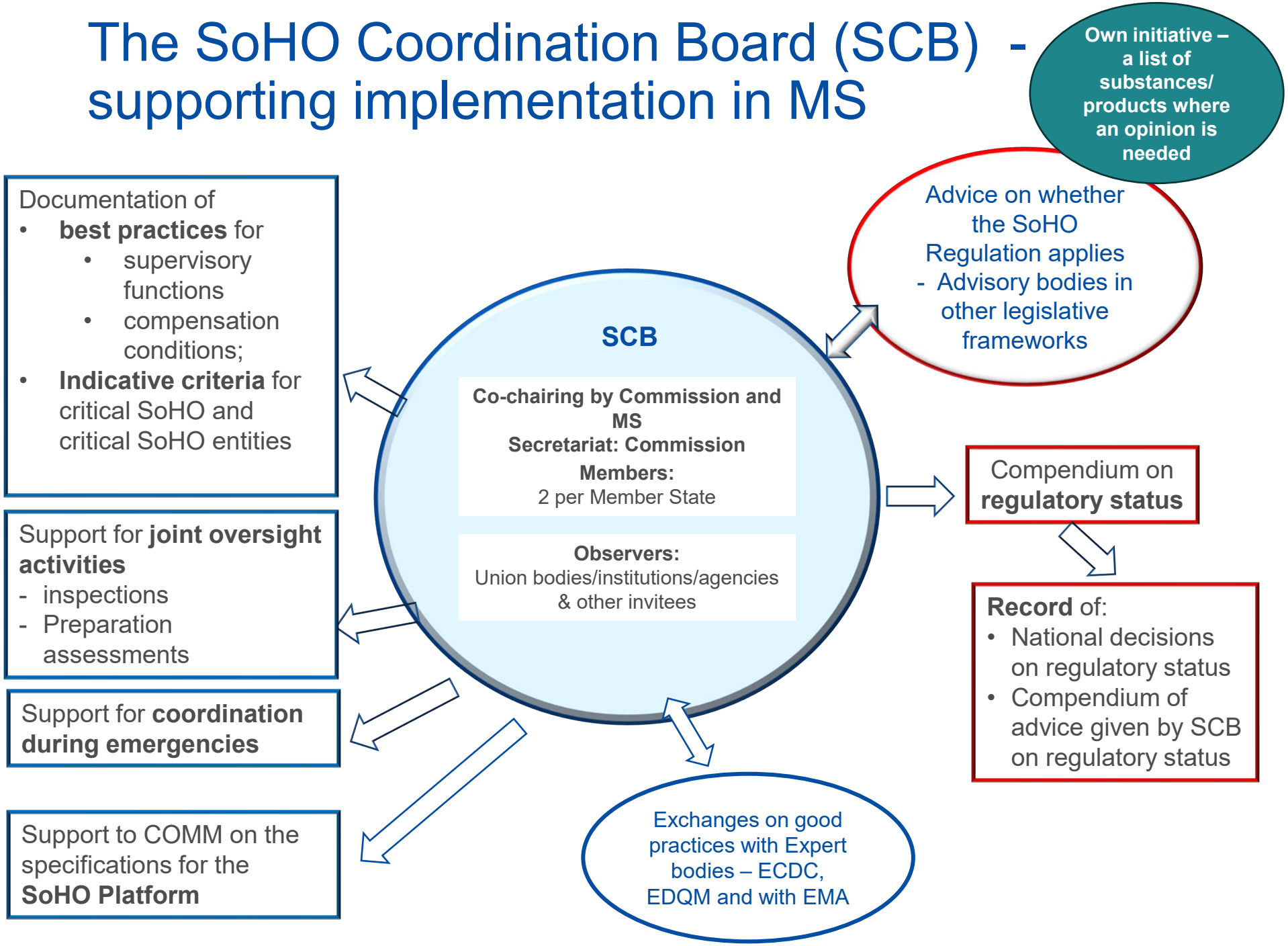
- SoHO donor registration
- SoHO donor history review and medical examination
- Testing of SoHO donors or persons from whom SoHO are collected for autologous or within-relationship use
- Collection
- Release

When carried out before distribution to a manufacturer, the following are also regulated by the SoHO Regulation:

- Storage; Distribution; Import; Export.

Art 2(7) – when the SoHO is used to manufacture an autologous medicinal product – only testing and collection are covered by SoHO Reg

The SoHO Coordination Board (SCB) - supporting implementation in MS

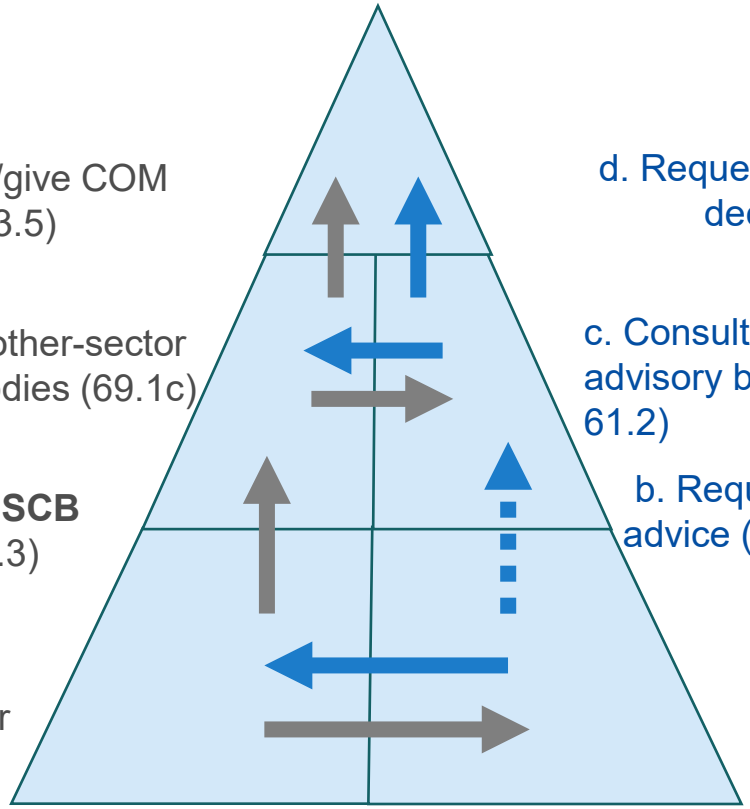


Building coherent Pharma/SoHO classification decisions and advice

3. If needed, COM decisions

2. If needed, EU-level advice

1. National decisions



Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
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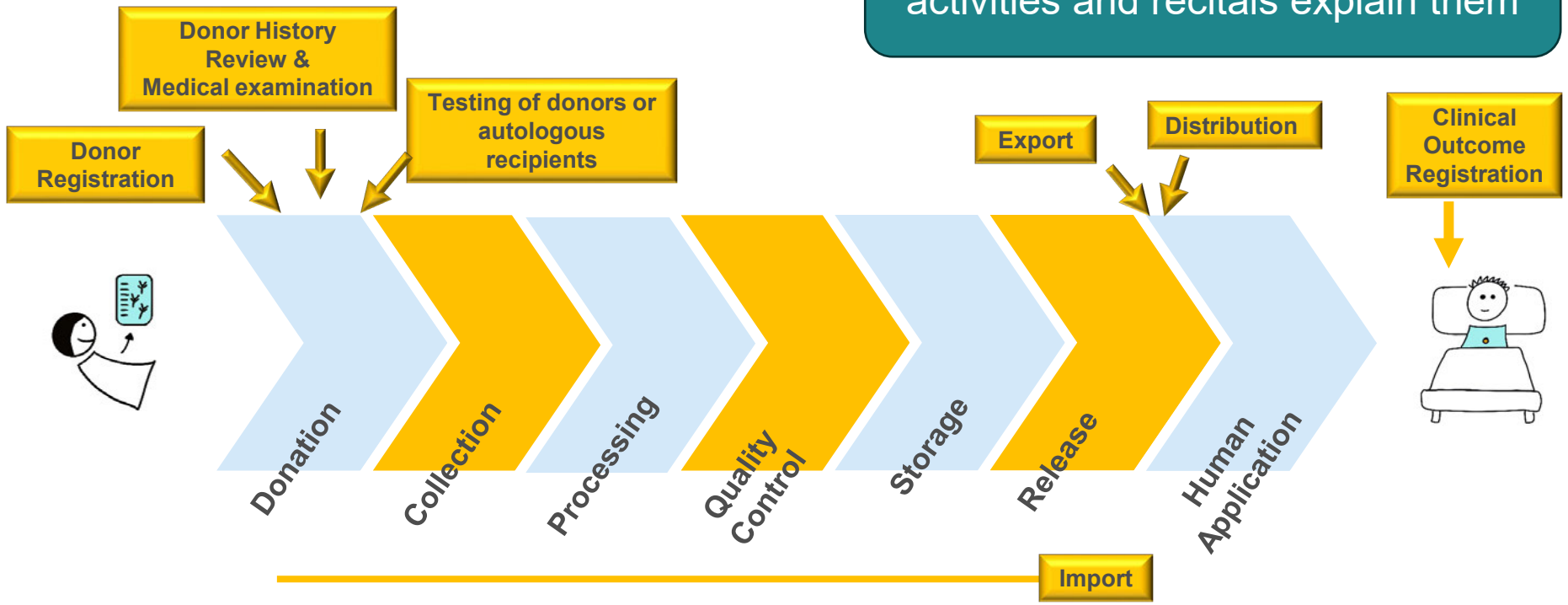
- Recipient and offspring protection
- Supply continuity
- Digitalisation – the SoHO platform

Supervision of all SoHO Activities that directly impact safety, quality or effectiveness

Definitions provided for the SoHO activities and recitals explain them



Any actor organising one or more SoHO activity/ies needs to register as SoHO entity with the Competent Authority

European Commission

….but risk-based authorisation, ensuring efficient use of authority resources

A **SoHO entity** carries out **one or more SoHO activities**

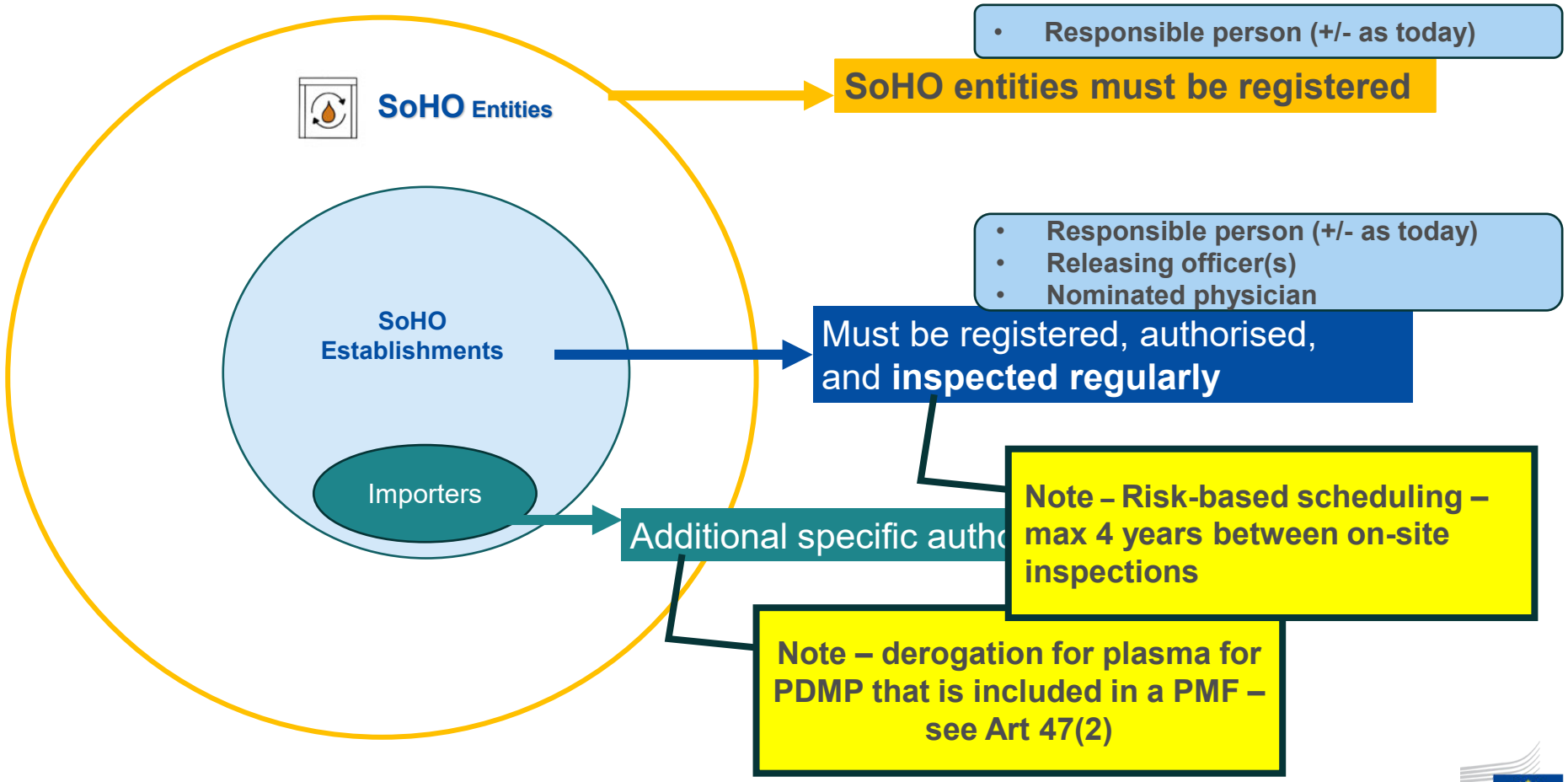
A **SoHO establishment is a SoHO entity that** carries out at least

- **Both processing and storage, or**
- **Release, or**
- **Import, or**
- **Export**

A SoHO establishment may carry out many other SoHO activities – all will be included in their authorisation

Note: ***CAs may regulate a SoHO entity as a SoHO establishment, even if it does not meet the criteria above, if it considers that the entity has a particularly important impact (e.g. a testing laboratory that tests donors for a whole region or country, a register that identifies and selects donors for one or more Member States).***

The concept of **SoHO entities** and **SoHO establishments:** graded approach to oversight - high level of transparency



Key new and changed concepts

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- Supply continuity
- Digitalisation – the SoHO platform

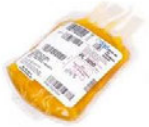
SoHO Preparation Authorisation – robust evidence of safety and effectiveness

What is a ‘SoHO Preparation’?

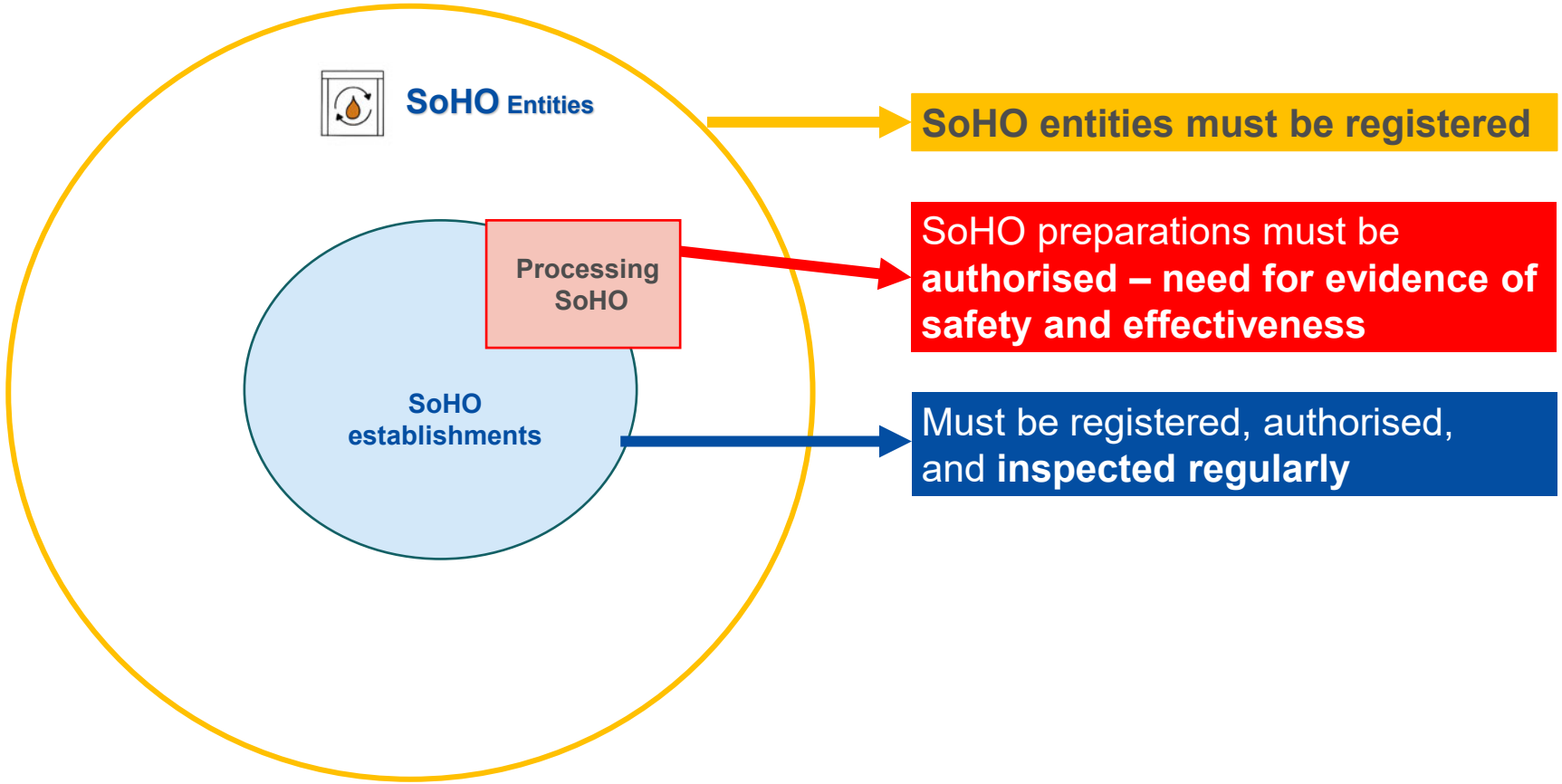
A particular SoHO that has been **subjected to processing,** and where relevant other SoHO activities, **has a specific clinical indication and is intended for immediate application to a recipient or for distribution.**

→ Must be **authorised**

EXAMPLE

SoHO	**SoHO Preparations**	
Blood	Plasma	
	Red blood cells	
	Platelets	

The concept of **SoHO entities** and **SoHO establishments:** graded approach to oversight - high level of transparency



SoHO Preparation Authorisation

Taking into account any relevant EDQM monograph

1 Systematic Benefit:Risk Assessment to determine the evidence available on safety, quality and effectiveness

2 Submission of an application, including laboratory validation and other safety, quality and effectiveness data and, where relevant, a clinical outcome monitoring plan proportionate to risk

3 Assessment of the application by the competent authority

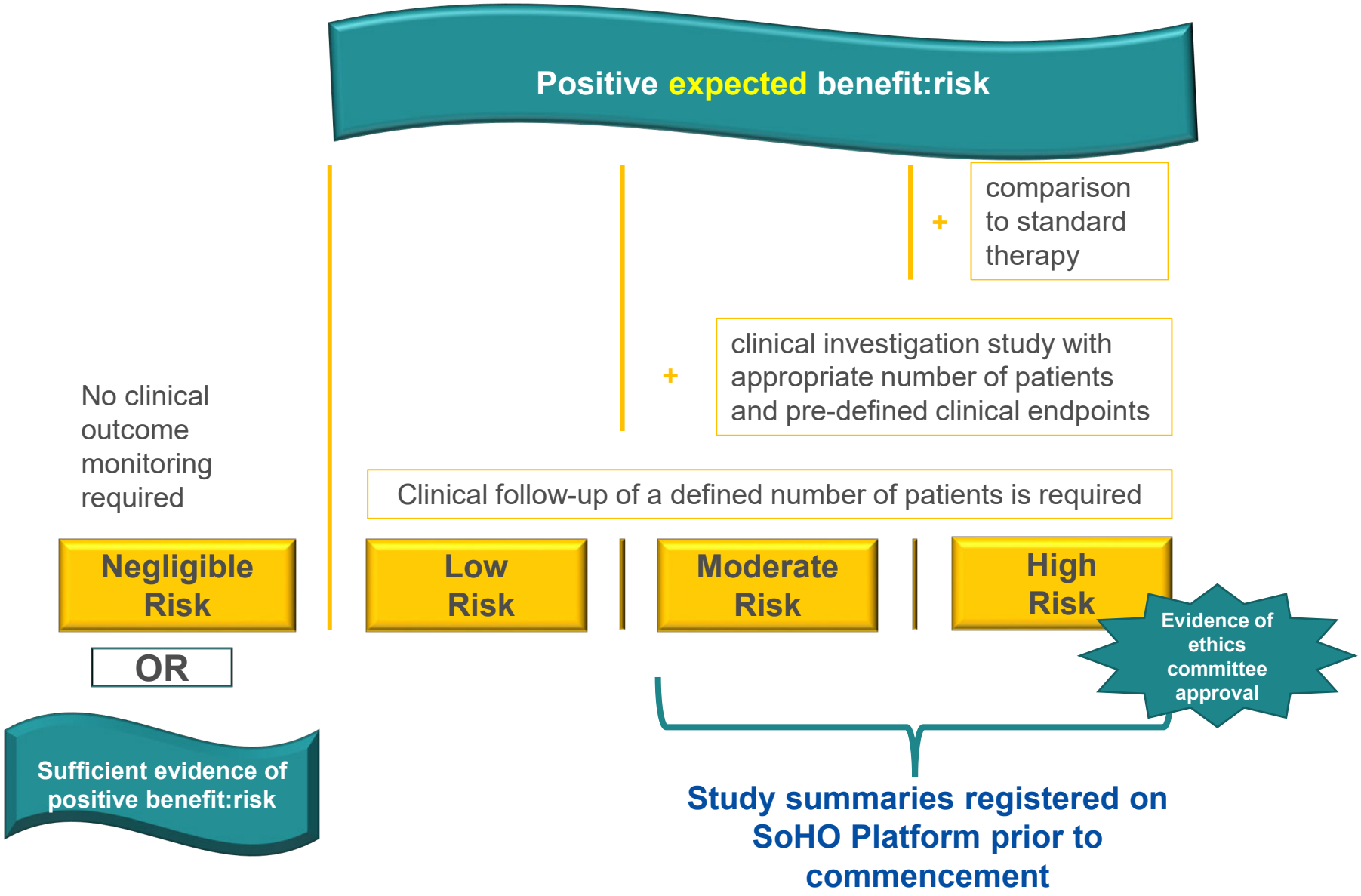
- Grant authorisation for the SoHO preparation
- OR
- Grant an approval of the Clinical Outcome Monitoring plan or request an amended plan
- OR
- Refuse authorisation

4 Assessment by the competent authority of evidence of safety, quality and effectiveness data gathered in clinical outcome monitoring

- Grant authorisation
- OR
- Refuse authorisation

Based on preparatory work done by GAPP Joint Action
(incl. stakeholders from 17 countries: 15 CAs & professional associations)

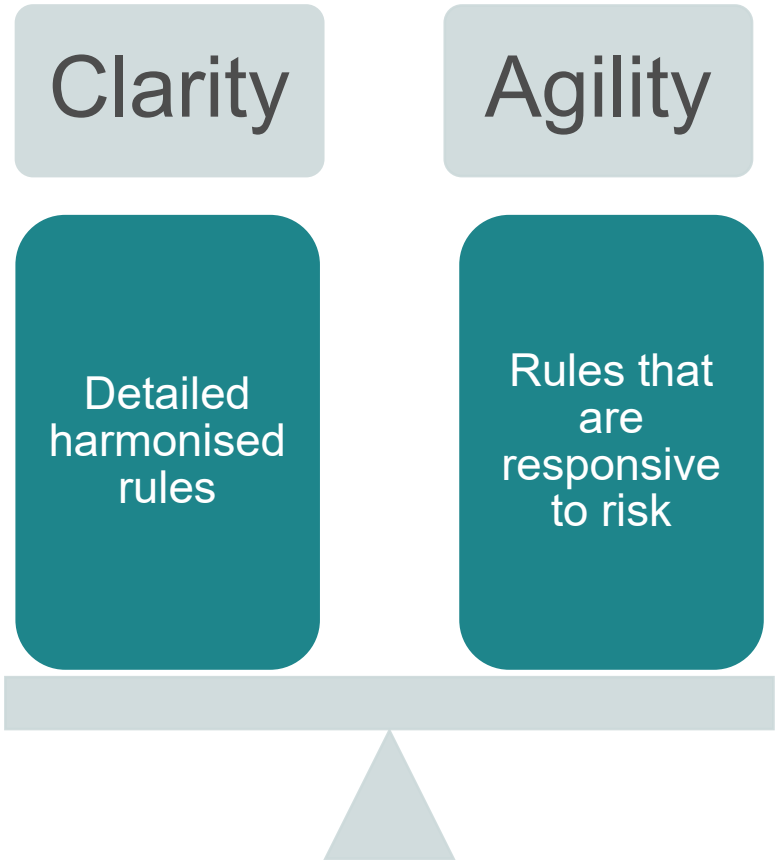
Clinical Outcome Monitoring Plans for gathering further evidence of safety and effectiveness in recipients

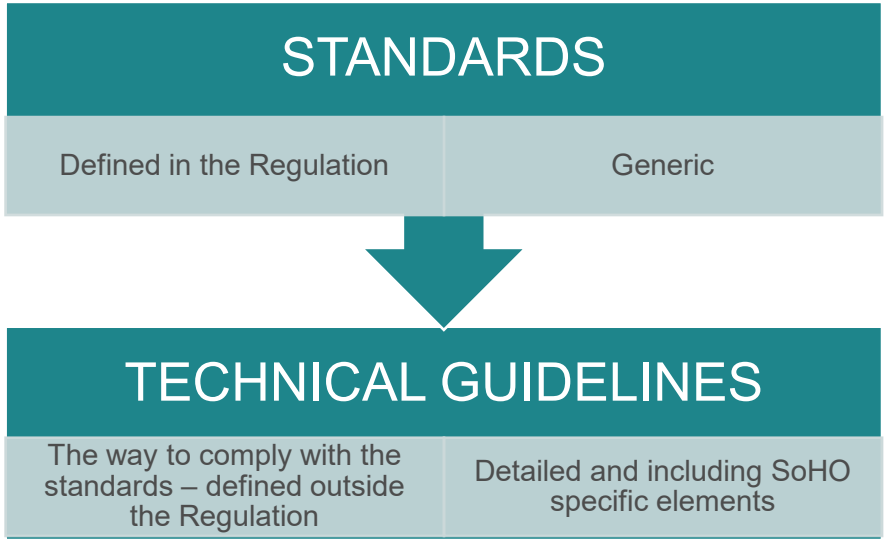


Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

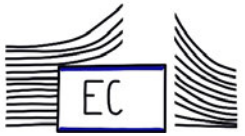
The challenge of setting technical rules





Implementation of generic standards through technical guidelines – **staying up-to-date with the science in an agile way**

Commission Implementing Legislation → "where the Commission deems necessary"



If none:

Technical Guidance on the EU SoHO Platform → Published & updated by ECDC/EDQM

OR:

"Equivalent" Guidance → Demonstrated by MS to achieve the standards in the Regulation

Inspectors shall deem the standards to be met

MS shall demonstrate compliance with standards – **may do so** by demonstrating equivalence to ECDC and EDQM

OR:

Other guidelines or methods based on international standards or scientific evidence

Entities shall demonstrate equivalence to inspectors – **may do so** by demonstrating equivalence to ECDC and EDQM

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
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- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

SoHO Donor Protection – significantly strengthened

Protection of SoHO living donors before, during, and after the collection.

- Including for donations by relatives
- Information & consent
- Physical and mental integrity, non-discrimination, data protection & safeguarding of anonymity (with some exceptions e.g. ID of MAR parents when allowed or obliged in MS)
- Donor health evaluation
- Risk-proportionate approach to donor monitoring: registration of donors subjected to
    - surgical procedures
    - medicinal product treatment
    - frequent or repeated donations implying risk to health.
- Required reporting of serious adverse reactions in donors

Protection of the dignity and integrity of SoHO deceased donors

- Information & consent by relatives, when applicable

Voluntary & Unpaid Donation

Principle maintained
Based on Recommendations of the Council of Europe Committee on Bioethics – aiming for financial neutrality

- **NO financial incentives or inducements** to donate
- **Compensation** of living donors for losses can be allowed in accordance with the principle of VUD
- When a Member State allows compensation – **upper limit to be set in national legislation** – transparent criteria based on best practices established by the SCB
- Compensation conditions set in MS to be **shared** with the other MS via the SCB
- Donation **promotion and publicity activities** must not refer to compensation (without prejudice to national laws on information provision)

Considerable elaboration of recitals (4) to explain provisions

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
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- Digitalisation – the SoHO platform

Recipient and offspring protection

- Identification and mitigation of risks from **transmissible infectious, genetic, malignant diseases**
- Identification and mitigation of risks from **toxins, contaminants** from the environment, other donations, the personnel, the equipment, reagents etc.
- Identification and mitigation of risks of **detrimental effects on inherent properties of the SoHO concerned**
- Identification and mitigation of risks of **harmful immune reactions**
- Application of national rules regarding the **maximum numbers of offspring** from one SoHO donor
- **No application of SoHO unnecessarily** or in cases where there is no proven benefit
- No promotion of SoHO application based on **misleading information**
- No human application of SoHO without therapeutic or assisted reproduction objective (i.e. **no exclusively cosmetic or nutritional applications**)

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

Competent Authorities: working together for improved oversight

Member States

Designate

One or more SoHO competent authorities

If just 1 CA is designated → it is also considered as the SoHO national authority

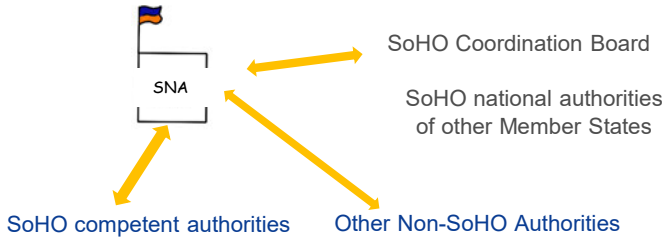
If more than 1 CA are designated → 1 among them to be designated as the SoHO national authority

Clearly defined principles on independence, impartiality and transparency

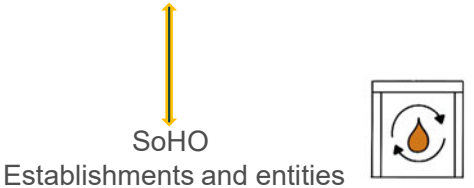
Note: Some SoHO supervisory activities can be delegated to delegated Bodies

Main Roles

SoHO national authority: Liaison & Cooperation



SoHO competent authorities: SoHO Supervisory Activities



Vigilance overview – largely unchanged

No change to SAR/SAE definitions!

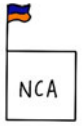
SoHO Entities

Send SAR/SAE notification & SAR/SAE investigation report to their CA

Competent Authorities

- Verify info of SAR/E notifications & investigation reports, assess the results of the investigation, inform the entity
- Send annual summary of SAR/E notifications & investigation reports received to their **SoHO National Authority**
- Launch **SoHO rapid alerts**

Communication with CAs from other frameworks



- Submits annual summary to the **EU SoHO Platform**
- Publishes aggregated summary for their MS

- Aggregate the summaries from the **SoHO National Authorities**
- publish annual SoHO vigilance report

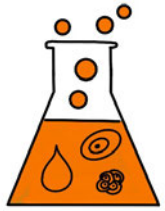
Vigilance enhancements

- Inclusion of SAR reporting requirement for SAR in **living SoHO donors**
- Clarification that **SAR/E detected during clinical outcome monitoring** must be reported
- Obligation for reasonable efforts to encourage recipients of MAR donations to communicate information on **genetic conditions in offspring** – when serious these are reportable as SAR
- **Role of ECDC** for SAR concerning infectious disease transmissions
- Formalisation of **communication** requirements with **CAs in other sectors**, when appropriate
- Clarification that **loss of critical SoHO** constitutes an SAE in defined situations
- CAs to provide **guidance and templates** to professionals and to **inform relevant SoHO entities of Rapid Alerts** received

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
- Recipient and offspring protection
- Vigilance
- Supply continuity
- Digitalisation – the SoHO platform

Resilience of Supply



Critical SoHO

'**Critical SoHO**' are SoHO that for which an insufficient supply will result in serious harm or risk of harm to patients or a serious interruption in manufacture of critical products regulated by other legislation.

A '**critical SoHO entity**' is a SoHO entity that carries out activities contributing to the supply of critical SoHOs and the scale of those activities is such that a failure to carry them out cannot be compensated by activities of other entities or alternative substances or products for recipients.

Supply of **critical SoHO** is protected by:

- **Obligations on Member States** to ensure a sufficient, adequate and resilient supply
  - Facilitate donation
  - Communication and education
  - Optimal use
- **Activity data collection** and monitoring
- Supply **alerts**
- National **SoHO emergency plans**
- SoHO Entity **emergency plans**
- **Derogations** and additional measures in emergency situations

New article!

Key new and changed concepts

- Scope and advice
- SoHO activities, entities and establishments
- SoHO Preparations and their authorisation
- Standards and hierarchy of technical guidelines
- Donor Protection and Voluntary Unpaid Donation
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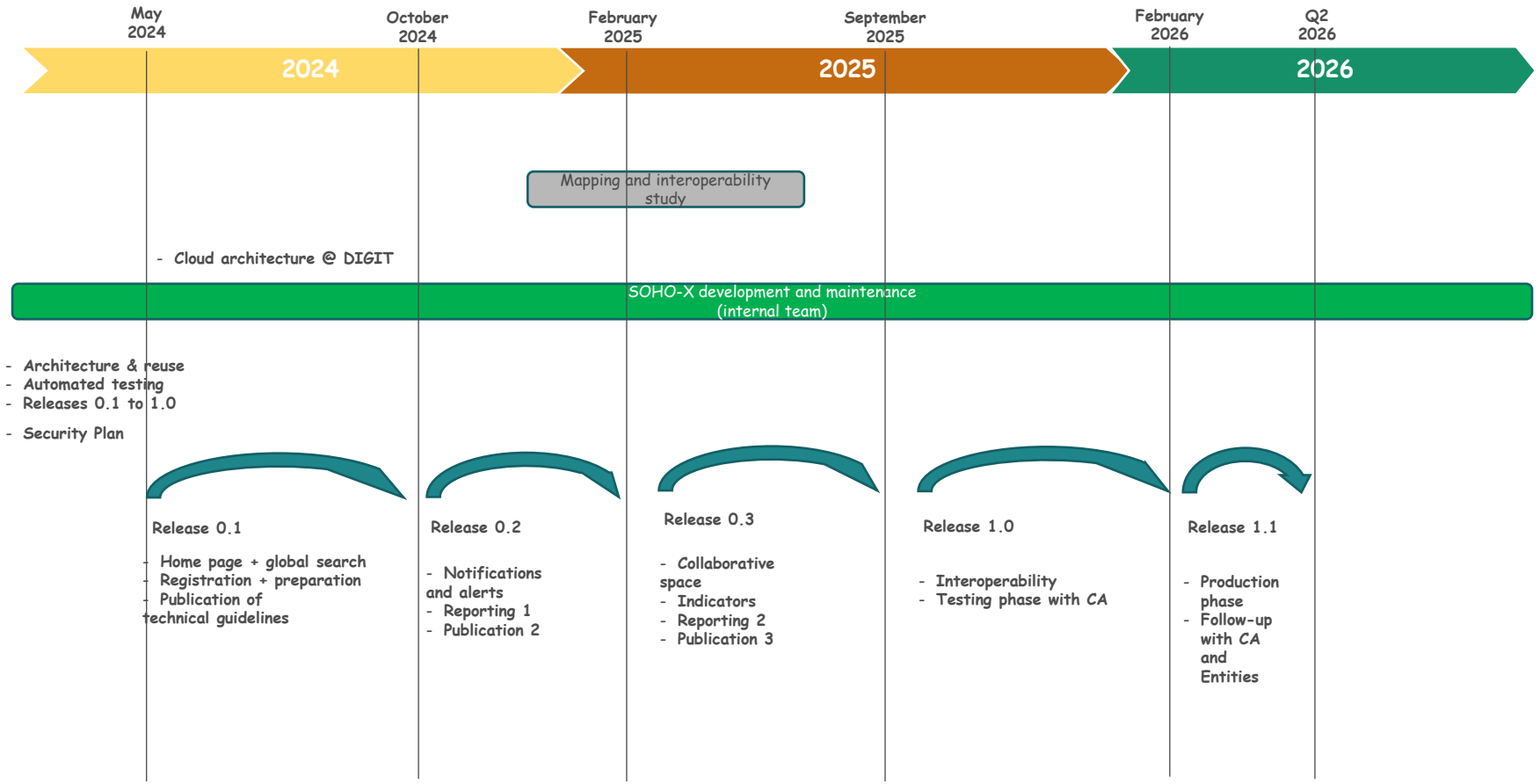
- Supply continuity
- Digitalisation – the SoHO platform

Digitalisation – efficiency, transparency, monitoring

SoHO Platform Roadmap



European Commission

Next steps
Entry into Force and Date of Application

- Formal approval by the Council and publication in the Official Journal
- The Regulation will enter into force 20 days after its publication in the Official Journal of the European Union – during **2024** (~ before summer)
- 3 years before the provisions become applicable - **2027** (an additional year for some provisions)

Current & future EU4H actions SoHO

Support implementation
Focus on implementation

Project name (year)	Scope
1. SUPPLY (2021)	Shortages, supply continuity (plasma)
2. EGALITE (2021)	Availability, accreditation (Tissues)
3. BRAVEST (2021)	Crisis resilience (Organs)
4. EuroTRACTOR (2021)	Outcome registry (HSC)
5. EUMAR (2021)	Outcome registry (MAR)
6. SIGHTSoHO (2021)	Training authorities (B, TC)
7. Cooperation Agreement EDQM (2021)	Guidelines, vigilance, support professionals, supply (B, TC, O)
8. Readership (2022)	New obligations entities in hospitals (B, TC)
9. GAPP-Pro (2022)	New obligations process authorisation (B, TC)
10. New SoHO Breast Milk (2023)	Implementation new requirements for Breast milk banks
11. New SoHO FMT (call will be relaunched in 2024)	Implementation new requirements for FMT
11. Paired kidney exchange (2023)	Organs
12. Cooperation Agreement EDQM (2024)	Guidelines, vigilance, support professionals, supply (B, TC, O)
13. SoHO-X ICT (2024)	SoHO digital platform – new Regulation (B, TC)
14. Support for Organisational by SoHO Authorities (call to be launched in 2024)	Support the implementation of the supervisory functions in the new SoHO regulation
15. Regulatory Coherence (call to be launched in 2024)	Topics of concern across EU frameworks

Thank you

Technical guidelines on the prevention of donor-derived transmission of communicable diseases through SoHOs

SoHO-Net Organs Group meeting – 18 June 2024

Context

REGULATION (EU) 2024/…

OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of …

on standards of quality and safety for substances of human origin intended for human application and repealing Directives 2002/98/EC and 2004/23/EC

(Text with EEA relevance)

Article 59, paragraph 4

For those standards, or elements thereof, concerning protection of SoHO recipientsand offspring from medically assisted reproduction for which no implementing acthas been adopted, SoHO entities shall *take into account*:

a) The most recent technical guidelines, as indicated on the EU SoHO Platform […] :

(i) published by the ECDC concerning the prevention of communicable disease transmission;

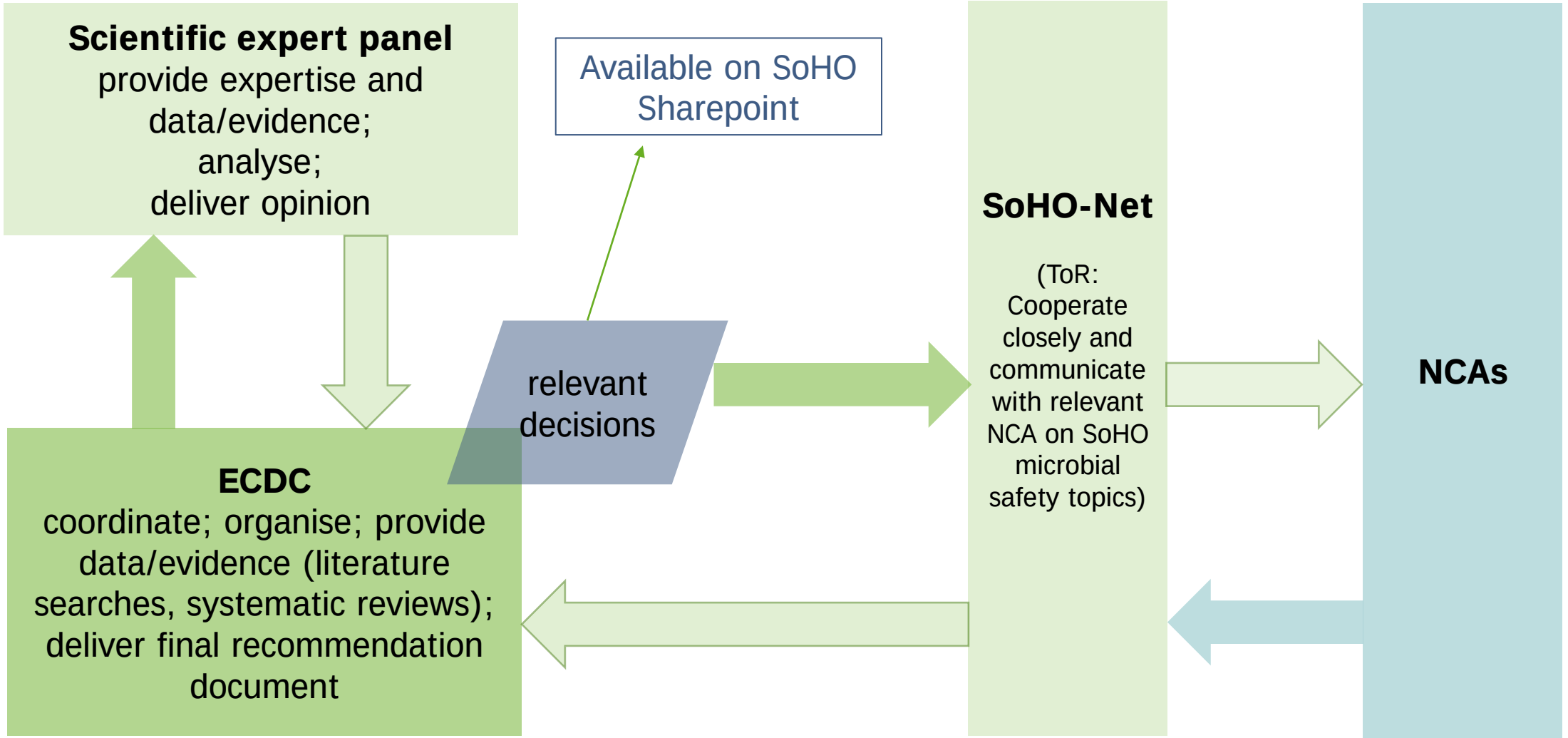
Of note: organs are excluded from the definition of SoHO from the scope of this regulation and thus of this project

Role of ECDC

- *Develop* and **publish technical guidelines concerning the prevention of donor-derived communicable disease transmission** through SoHO application
- Cover **relevant pathogens for SoHO**: those listed in the current directives and those with current acute relevance (e.g., Dengue virus)
- For SoHOs as defined in the Regulation (i.e., not including organs)
- Supported by an **ad hoc scientific expert panel(s)**

The development of technical guidelines follows internal ECDC procedures approved by ECDC's Advisory Forum

Overall project plan



Guideline content development process

- The **expert panel is** ultimately **expected to provide feedback** on statements regarding:
  - Testing strategies
  - Deferral strategies (including deferral periods)
  - Testing methods
- The feedback of the panel **serves as a basis for ECDC to draft the guidelines**
- The draft guidelines will be submitted for review to ECDC advisory forum, SoHO-Net, EDQM, EMA, WHO and to other relevant stakeholders (closed consultation)

ECDC SoHO guidelines – update
Overview

Expert panel meetings

- HIV: Sept 23–Feb 24

- HBV/HCV: May 24–Sept 24 (next meeting: 03 July)

- *T. pallidum*: Dec 24–May 25

HIV Guideline draft and review

- Drafting February to June 2024

- SoHO-Net review: June to August 2024

  ➔ SoHO-Net should liaise with NCAs

- External stakeholder consultation: November-December

Publication

Current plan:

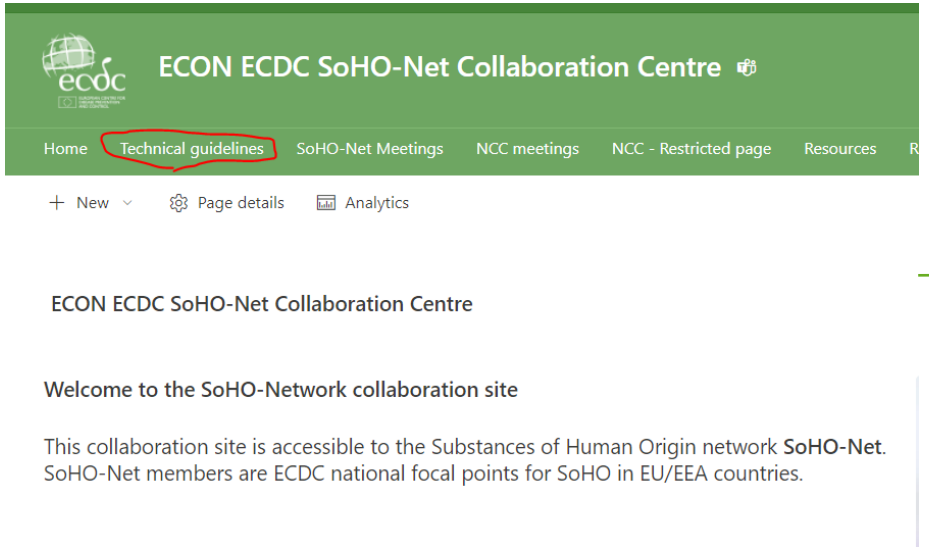
- HIV: March 2025

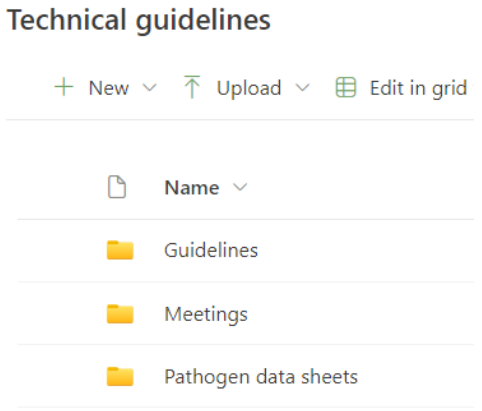
- HBV/HCV: End 2025

- *T. pallidum*: 2026

Note: timelines are according to current plan

ECON ECDC SoHO-Net Collaboration Centre





- Guidelines: draft guidelines for SoHO-Net review
- Meetings: “short minutes” of expert panel with decisions and agreements
- Pathogen data sheets: Latest versions of the evidence base for the guidelines

Thank you

ECDC guidelines
Recommendations for donor testing for HIV and HBV/HCV in SoHOs other than solid organs

Flávia Cunha, ECDC

Stockholm, 18 June 2024

Context

- Which **risks of exposure** are relevant for SoHO safety?
- **Which** SoHO donors should be tested?
- **When** to test?
- Which laboratory **screening tests** should be used?
- **What to do** in case of reactive screening tests?
- What **deferral period** should be considered?

Context

Expert panel meetings

- HIV: Sept 23–Feb 24

- HBV/HCV: May 24–Sept 24 (next meeting: 03 July)

- *T. pallidum*: Dec 24–May 25

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- SoHO-Net review: June to August 2024

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Publication

Current plan:

- HIV: March 2025
- HBV/HCV: End 2025
- *T. pallidum*: 2026

Risks of exposure to HIV

Recent risks of exposure to HIV **should be** considered when assessing donor eligibility.

Deferral period in case of recent risk of exposure to HIV

- **At least 8 weeks** since the last event with a risk of exposure to HIV.
- Exceptions: oral PrEP or PEP - 12 weeks | injectable PrEP – 24 months.

- **Deceased donors** → not applicable; test results not reliable and risks of exposure to HIV should be considered.

Risks of exposure to HIV

It is **advised** to consider the following risks of exposure to HIV:

Active sexually transmitted infection (STI)
Condomless anal sex with a new partner
Condomless anal sex with more than one partner
Condomless sex with a partner infected with HIV
Condomless sex with a partner using injectable drugs
Condomless sex with a partner using PrEP or PEP
Condomless sex with a partner with an active STI
Needle sharing and/or injecting drug use
Transactional sex in a country with a higher HIV prevalence than in the EU/EEA
Use of injectable PrEP
Use of oral PrEP or PEP

Donor testing – HIV – Tissues/Deceased donors

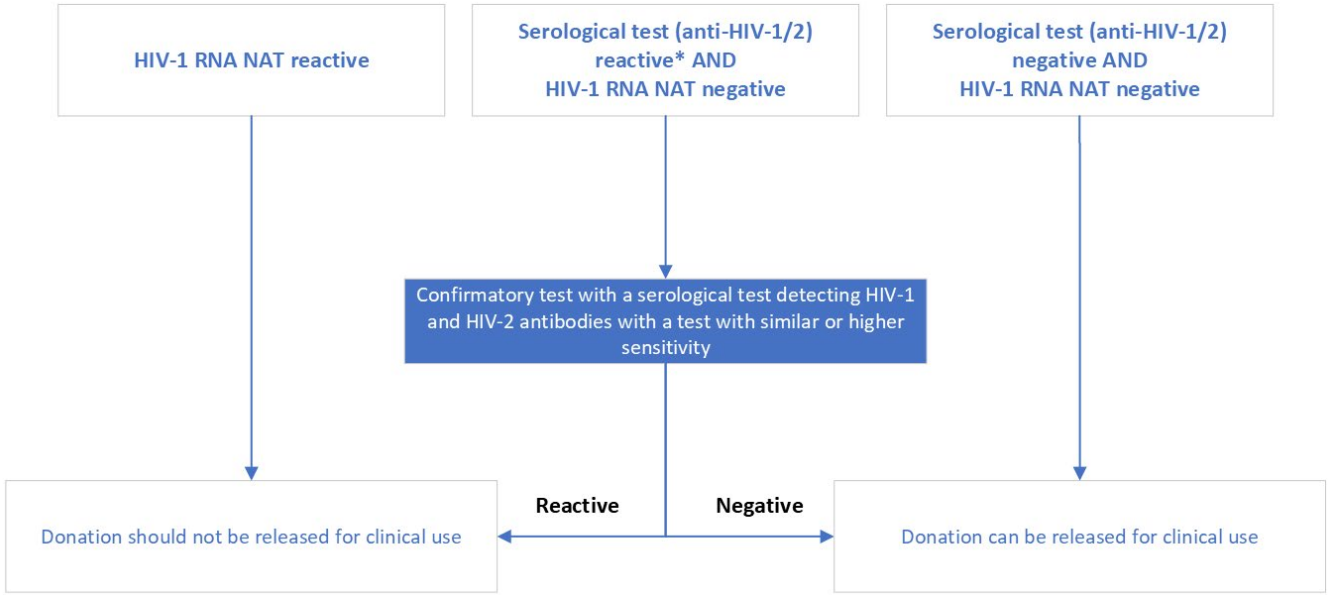
REQUIRED

Testing of donors

- All donors, at donation, should be tested for HIV.

Screening tests

- NAT detecting HIV-1 RNA + anti-HIV-1/2.
- NAT should have two targets in the HIV genome.
- NAT 95% Limit of detection (LOD): ≤50 HIV RNA copies/ml.



* Reactive is defined as repeat reactive if the serological test is repeated. If the serological test is initially reactive and negative in retesting, the donation can be considered negative provided the NAT is also negative.

Donor testing – HIV – Tissues/Deceased donors

ADVISED

Screening tests

- Use of NAT detecting both HIV-1 **and** HIV-2 RNA.

Outcome of test results

- Retest initially reactive anti-HIV-1/2 → retest with the same assay and in the same sample.
- **No need** to retest reactive NAT.

Practical consideration:

- Antigen-antibody (Ag-Ab) combination tests instead of Ab-only tests.

Donor testing – HIV – Tissues/Living donors

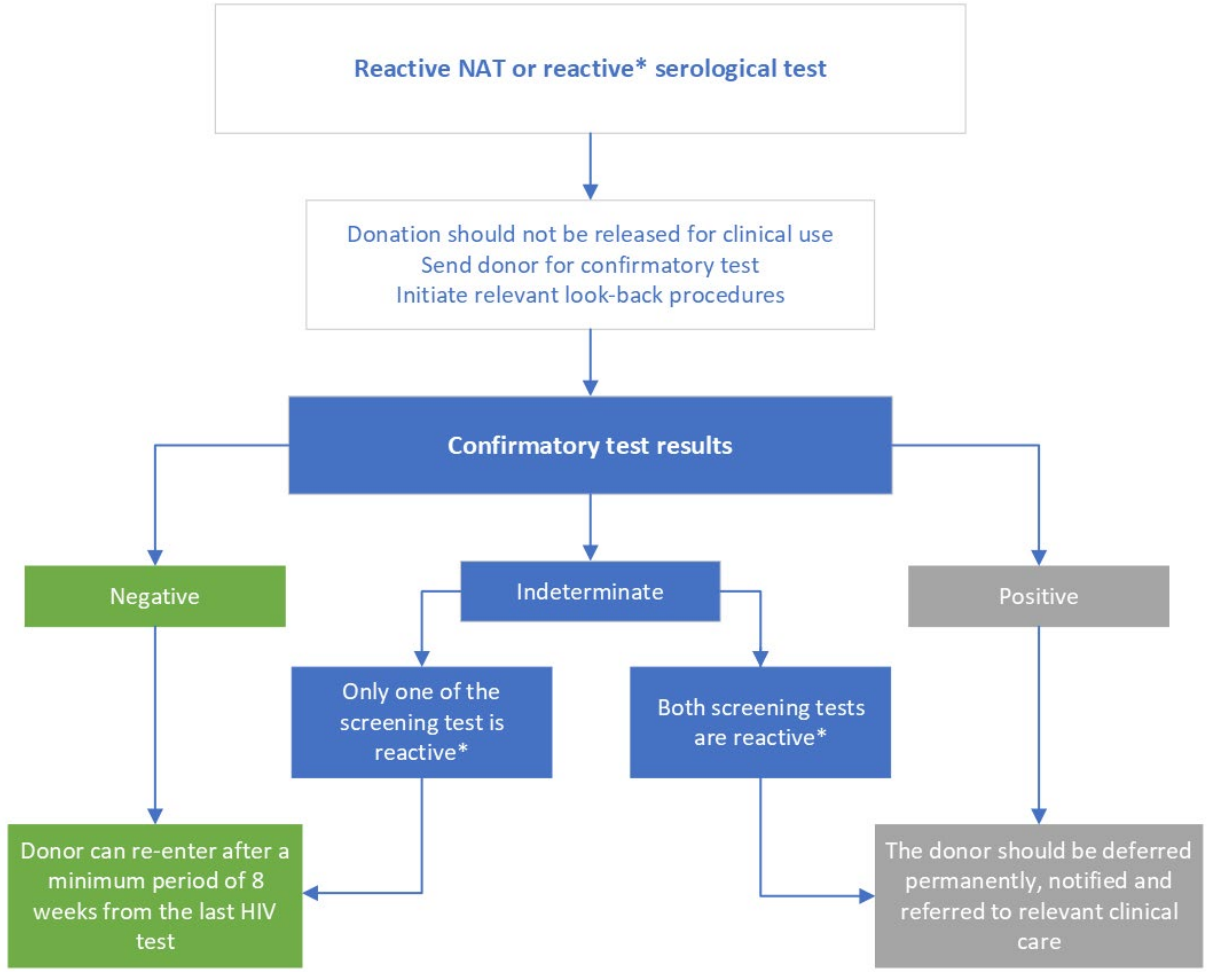
REQUIRED

Testing of donors

- All donors, at each donation, should be tested for HIV.

Screening tests

- NAT detecting HIV-1 RNA + anti-HIV-1/2.
- NAT should have two targets in the HIV genome.



Donor testing – HIV – Tissues/Living donors

ADVISED

Screening tests

- Use of NAT detecting both HIV-1 **and** HIV-2 RNA.
- NAT 95% LOD ≤ 50 HIV RNA copies/mL

Outcome of test results

- Retest initially reactive anti-HIV-1/2 → retest with the same assay and in the same sample.
- **No need** to retest reactive NAT.
- If first confirmatory test positive or indeterminate → second confirmatory test on a separate sample.

Practical consideration:

- Ag-Ab combination tests can be used instead of Ab-only tests.

Donor testing - HBV

- First panel meeting on 07 May 2024.
- List of risks of exposure to HBV assessed, but still open for further discussion.

TESTING STRATEGY

For all SoHOs:

All donors should be tested for HBV at each donation.

Donor testing - HCV

- First panel meeting on 07 May 2024.
- List of risks of exposure to HCV assessed, but still open for further discussion.

TESTING STRATEGY

For all SoHOs:

All donors should be tested for HBV at each donation.

Thank you!

The impact of the SoHO-regulation on organs safety – horizon scanning

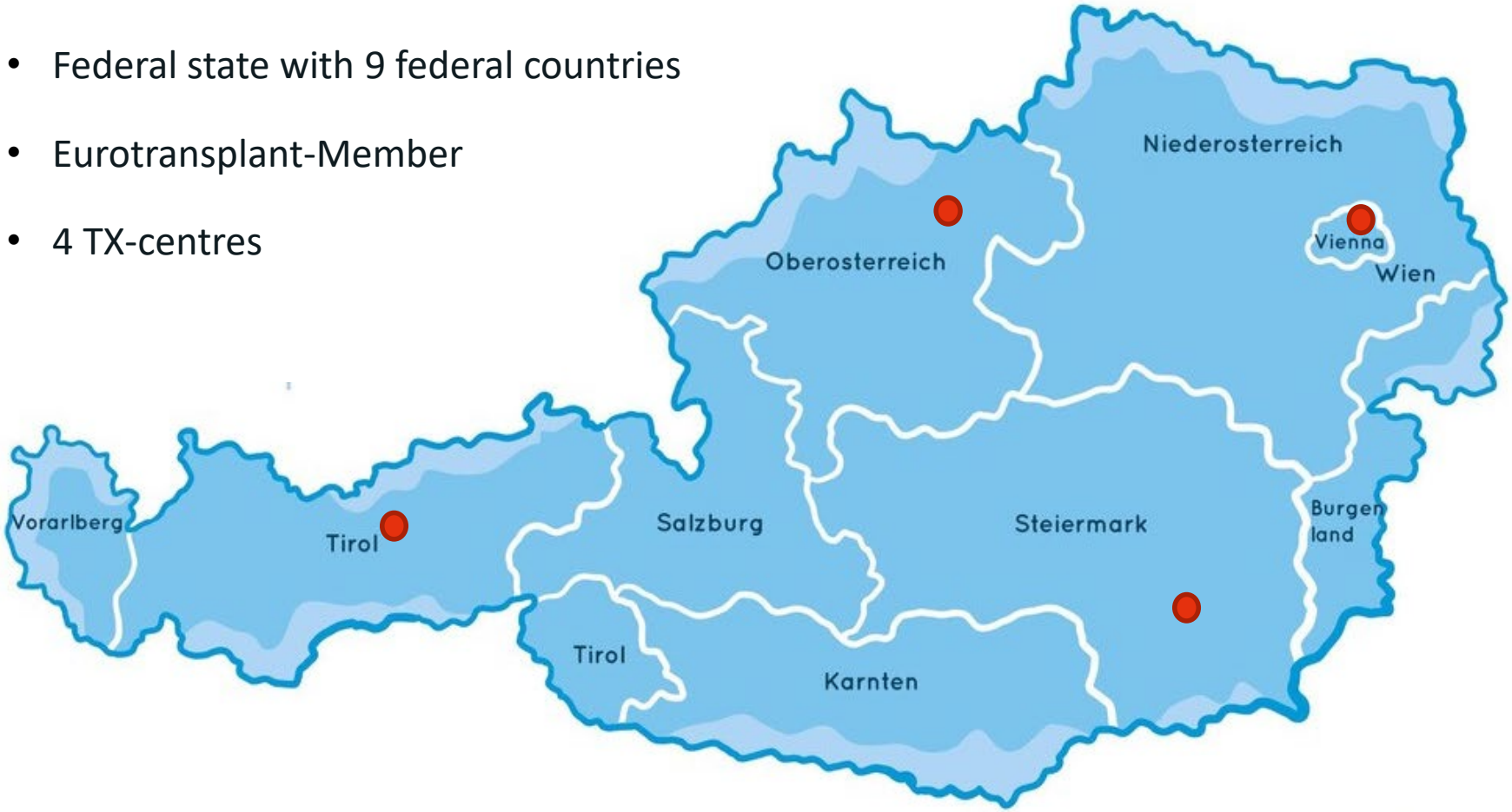
ECDC – NFP Organ meeting 18., 19.6.2024

Martina Brix-Zuleger
Federal Ministry of Social Affairs, Health, Care and Consumer Protection
Stockholm, 18th June 2024

Federal Ministry
Republic of Austria
Social Affairs, Health, Care
and Consumer Protection

General conditions in Austria

- Federal state with 9 federal countries
- Eurotransplant-Member
- 4 TX-centres



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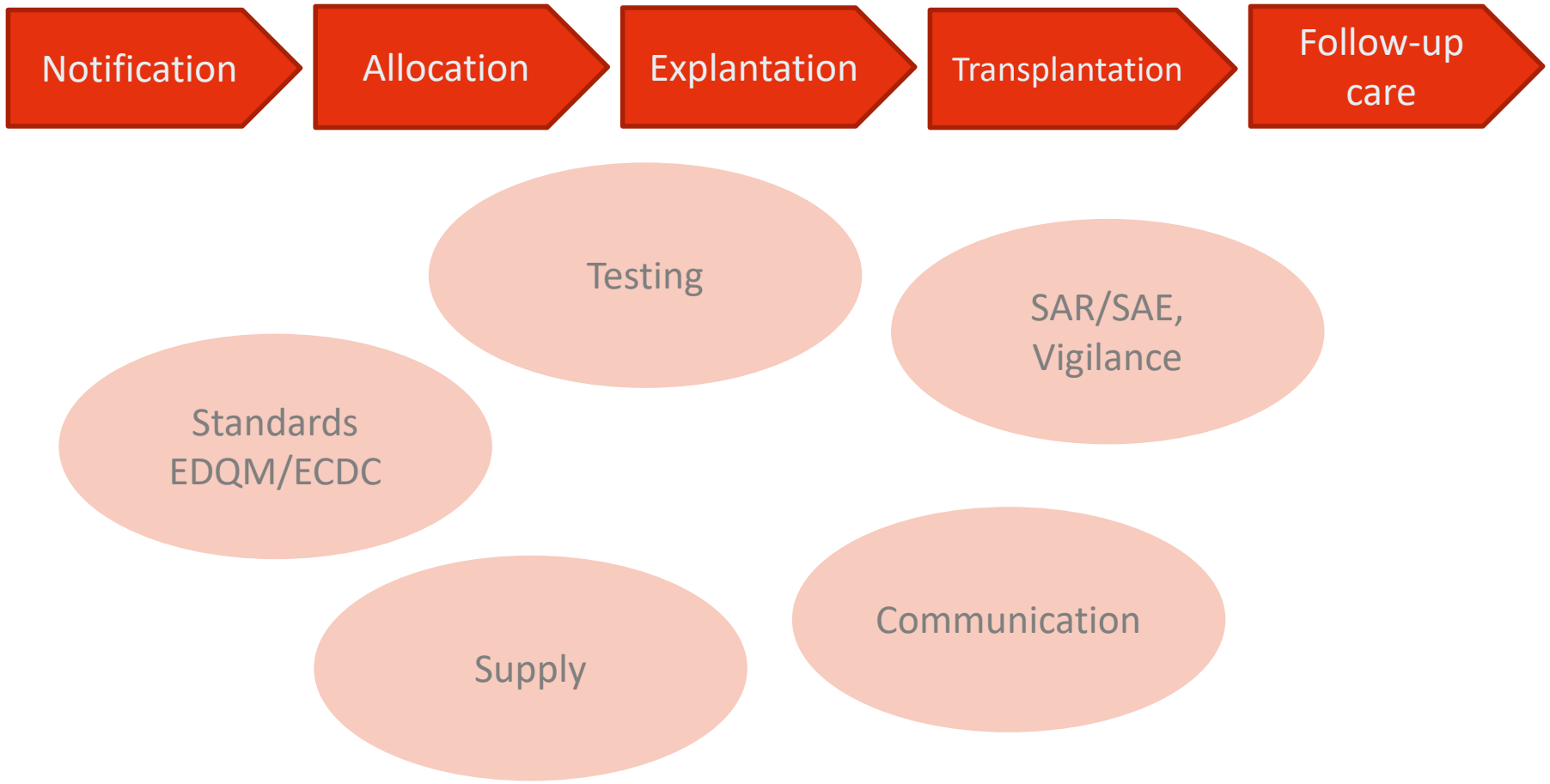
Federal Ministry
Republic of Austria
Social Affairs, Health, Care
and Consumer Protection

Interface SoHO-regulation and organs

- Physiological:
  - Vessels
  - Stemcells
  - Subsidiary tissues- and/or cell collection, e.g. valvular, bones, skin
  - Blood transfusions
- Effectings:
  - Vigilance: SAR, SAE
  - Communication
  - Supply

Federal Ministry
Republic of Austria
Social Affairs, Health, Care
and Consumer Protection

Horizon scanning



Federal Ministry
Republic of Austria
Social Affairs, Health, Care
and Consumer Protection

Conclusion

Possible effects of the SoHO-regulation on the organ area:

- optimizing the treatment of patients and
- increasing the safety for transplantpatients

but → we have to work together

Federal Ministry
Republic of Austria
Social Affairs, Health, Care
and Consumer Protection

Coming together is a beginning; keeping together is progress; working together is success.

Edward Everett Hale

Martina Brix-Zuleger
Federal Ministry of Social Affairs, Health, Care and Consumer Protection
martina.brix-zuleger@sozialministerium.at

Session 4
Hepatitis
18 June

Session overview

1. **Epidemiological overview of Hepatitis (B and) C in EU/EEA** – Ndeindo Ndeikoundam Ngangro, ECDC
2. **Questions and answers** – All

Sharing of experience with hepatitis C positive donors in Member States

3. **France** – Corinne Antoine, Agence de la biomédecine, France
4. **Italy** – Paolo Antonio Grossi, NFP Italy
5. **Discussion** – All

Epidemiological overview of Hepatitis B and C in EU/EEA

Ndeindo Ndeikoundam Ngangro, Ana Paula Finatto-Canabaro and Erika Duffell, ECDC

ECDC SoHO-Net meeting for Organs
18-19th June 2024

Global epidemiological situation of hepatitis B and C in 2022

Hepatitis B	Hepatitis C
254 million with chronic hepatitis B	50 million with chronic hepatitis C
1.2 million new hepatitis B infections/year	1 million new hepatitis C infections/year
1.1 million deaths from hepatitis B	0.2 million deaths from hepatitis C

Source: Global hepatitis report 2024: action for access in low- and middle-income countries. Geneva: World Health Organization; 2024. Licence: CC BY-NC-SA 3.0 IGO.
https://www.who.int/publications/i/item/9789240091672

The burden of viral hepatitis B and C in the EU/EEA

3.6 million people living with chronic HBV

(2016 estimate)

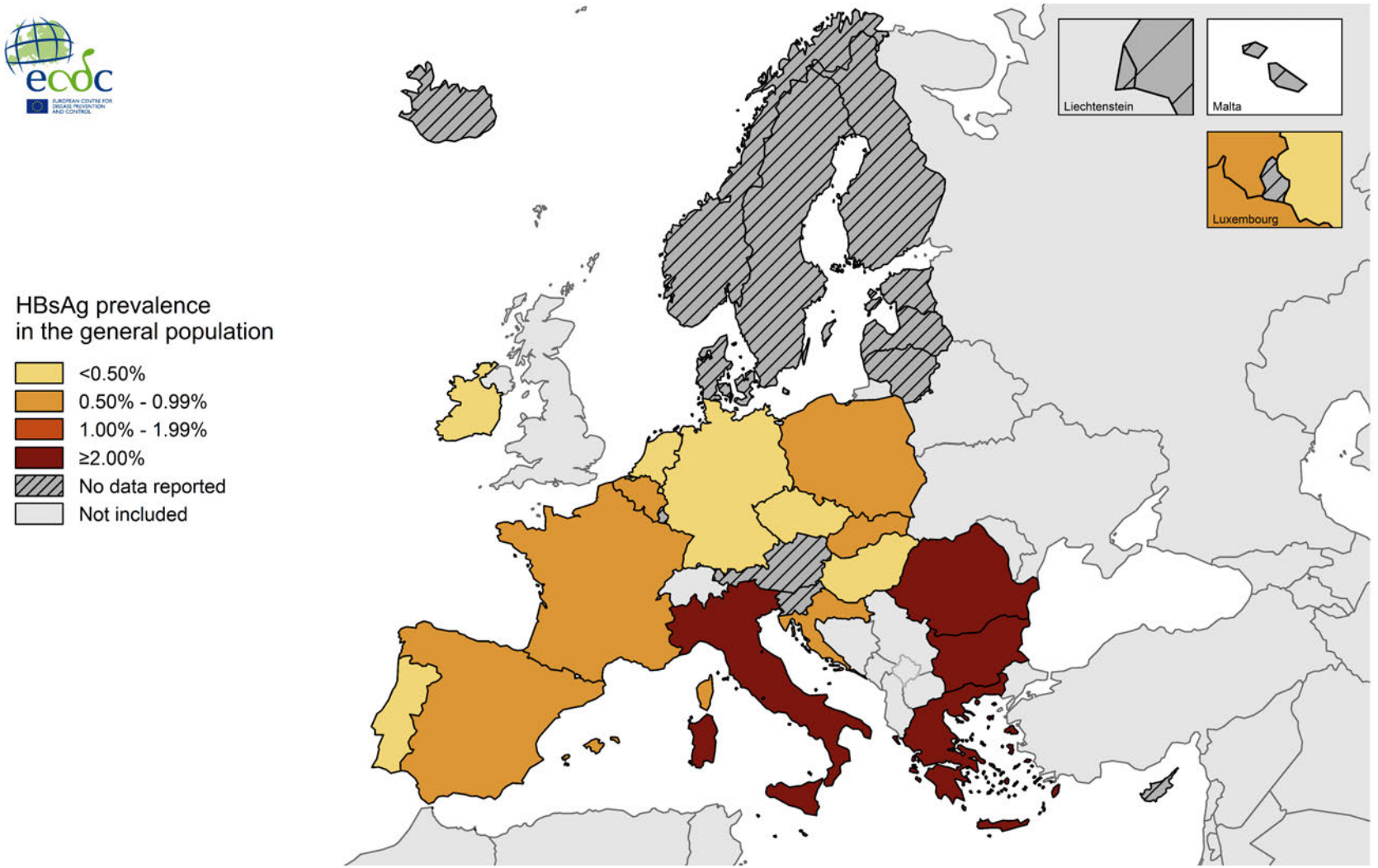
1.8 million people living with chronic HCV

(2022 estimate)

Variation in disease burden across countries and between different population groups

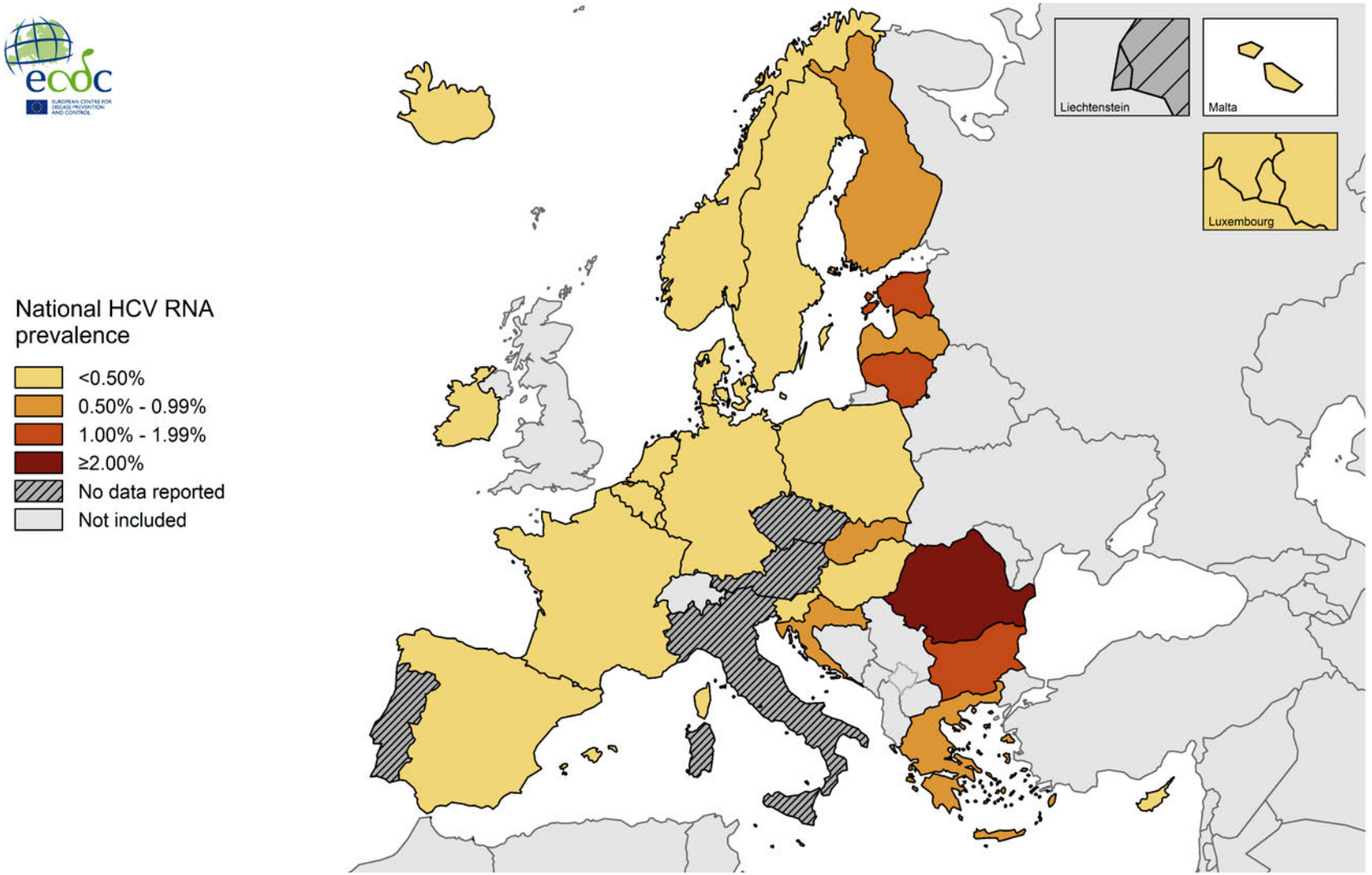
Source: Bivegete S et al. Estimates of hepatitis B virus prevalence among general population and key risk groups in EU/EEA/UK countries: a systematic review. Eurosurveillance, 28, 2200738 (2023), https://doi.org/10.2807/1560-7917.ES.2023.28.30.2200738
. Thomadakis C, Gountas I, Duffell E, Gountas K, Bluemel B, Seyler T, et al. Prevalence of chronic HCV infection in EU/EEA countries in 2019 using multiparameter evidence synthesis. Lancet Reg Health Eur. 2023 Dec 13;36:100792. doi: 10.1016/j.lanepe.2023.100792.

Hepatitis B (HBsAg) prevalence (%) in the adult general population in the EU/EEA, 2021



Source: *Bivegete S et al. Estimates of hepatitis B virus prevalence among general population and key risk groups in EU/EEA/UK countries: a systematic review.* Eurosurveillance, 28, 2200738 (2023), https://doi.org/10.2807/1560-7917.ES.2023.28.30.2200738

Hepatitis C (RNA) prevalence (%) in the overall population in EU/EEA countries, 2022



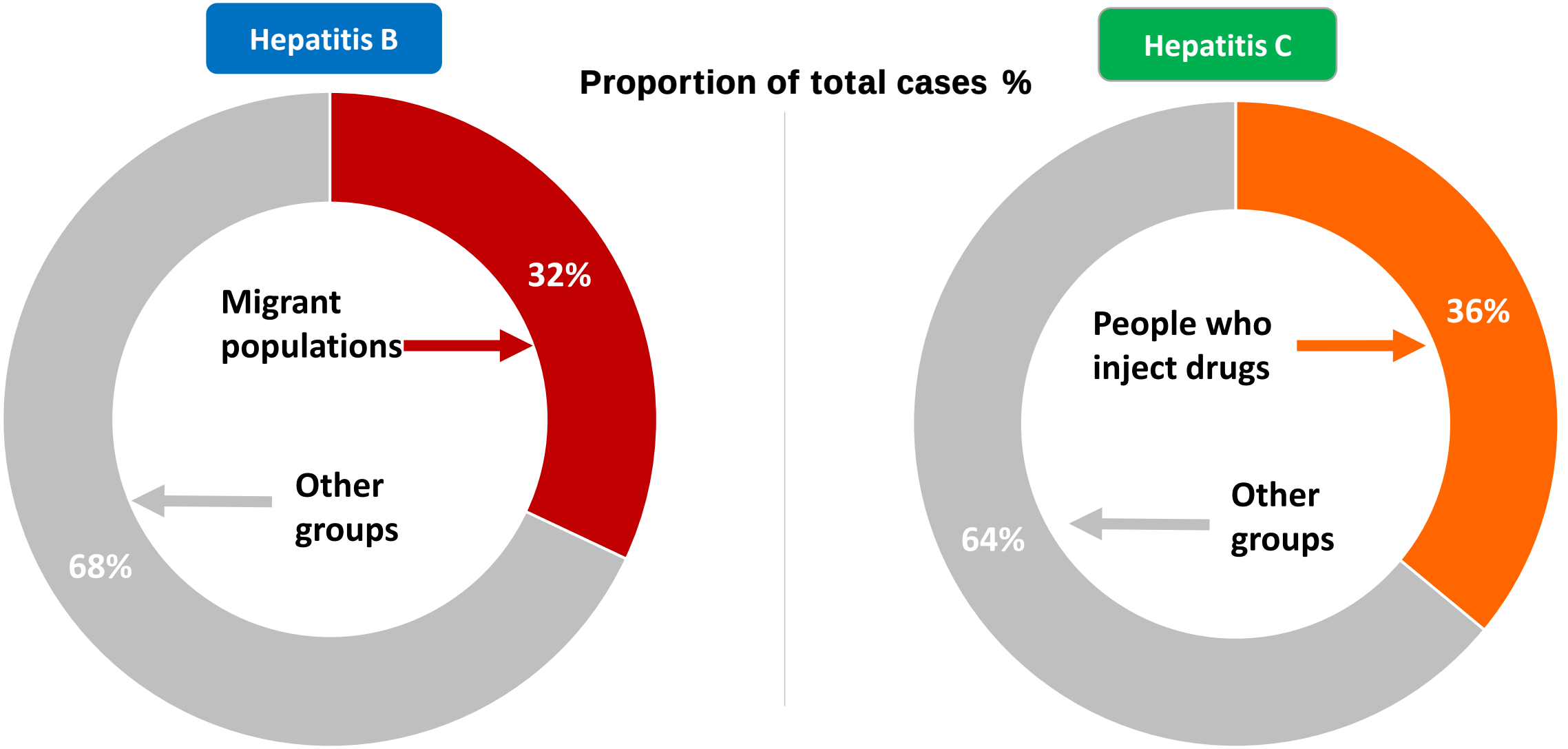
Source: Thomadakis C, Gountas I, Duffell E, Gountas K, Bluemel B, Seyler T, et al. Prevalence of chronic HCV infection in EU/EEA countries in 2019 using multiparameter evidence synthesis. Lancet Reg Health Eur. 2023 Dec 13;36:100792. doi: 10.1016/j.lanepe.2023.100792..

Prevalence of hepatitis B and C in key population groups

Hepatitis B (HBsAg prevalence)	Hepatitis C (anti-HCV)
Migrant populations 0.9 - 31.7%	People who inject drugs 15.4 – 96.8% (RNA prevalence 15.0 – 64.2%)
People who inject drugs 0 - 16.9%	People in prison 2.3 – 82.6%
People in prison 0.3 - 8.3%	Migrant populations 0 – 16.8%
Men who have sex with men 2.3 - 4.3%	Men who have sex with men 0.6 – 4.8%

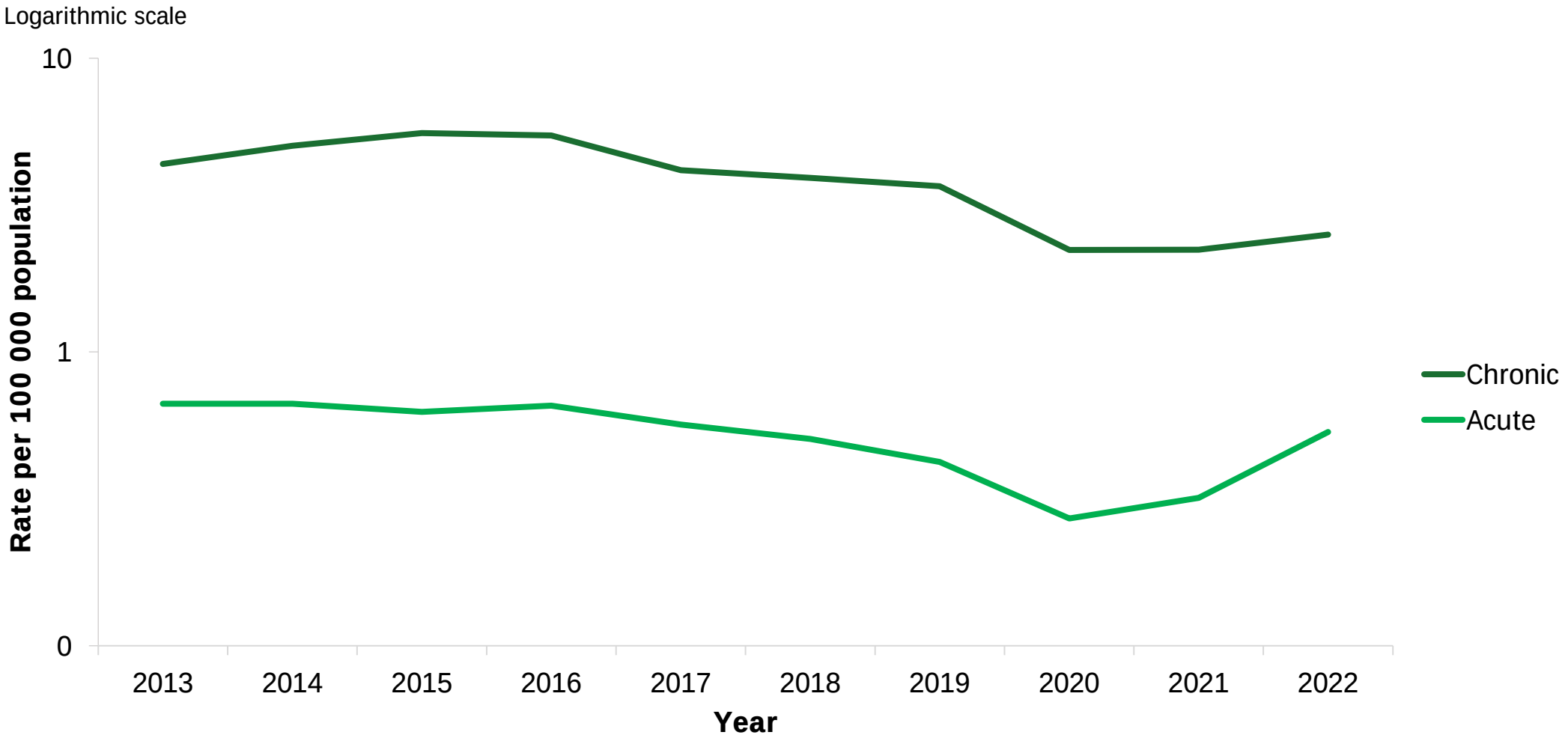
Source: Bivegete S et al. Estimates of hepatitis B virus prevalence among general population and key risk groups in EU/EEA/UK countries: a systematic review. Eurosurveillance, 28, 2200738 (2023), https://doi.org/10.2807/1560-7917.ES.2023.28.30.2200738. Christos T et al. National estimates of the prevalence of chronic HCV infection in EU/EEA countries in 2019 using multiparameter evidence synthesis. Awaiting publication in Lancet. EMCDDA Viral Hepatitis Elimination Barometer https://www.emcdda.europa.eu/publications/html/viral-hepatitis-elimination-barometer_en; ECDC hepatitis C prevalence data base https://www.ecdc.europa.eu/en/infectious-disease-topics/z-disease-list/hepatitis-c/tools/hepatitis-c-prevalence-database; Nakitanda et al. Hepatitis C virus infection in EU/EEA and United Kingdom prison: opportunities and challenges for action https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7650151/pdf/12889_2020_Article_9515.pdf.

Key populations affected by hepatitis B and C across EU/EEA countries



Source: HBV estimate – Canabarro APF et al Chronic hepatitis B infections in the European Union: estimates of prevalence using the workbook methodology (awaiting publication). HCV estimate - Thomadakis C et al. Prevalence of chronic HCV infection in EU/EEA countries in 2019 using multiparameter evidence synthesis. Lancet Reg Health Eur. 2023 Dec 13;36:100792.

Notification rates of acute hepatitis B per 100 000 population in EU/EEA countries, 2022

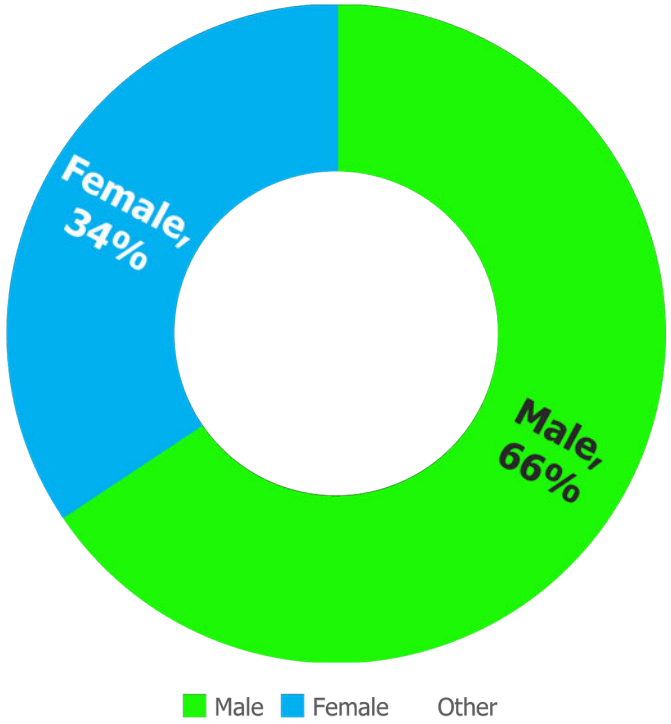


Source: ECDC (2024). Acute cases: Country reports from Austria, Cyprus, Czechia, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden.* Chronic cases: Country reports from Austria, Cyprus, Denmark, Estonia, Finland, Ireland, Latvia, Luxembourg, Malta, the Netherlands, Norway, Portugal, Romania, Slovakia, Slovenia and Sweden

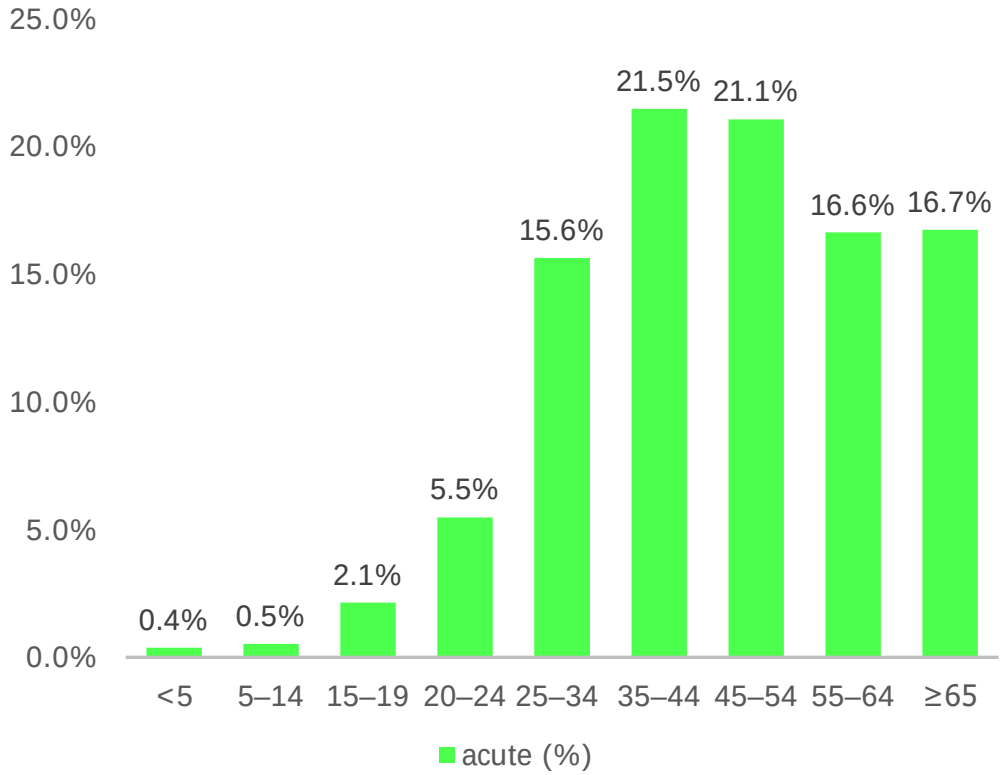
Acute hepatitis B notifications – by age and gender, EU/EEA, 2022

1 971 notified acute cases from 24 MS

GENDER (n=1 971)



AGE GROUPS (n=1 919)

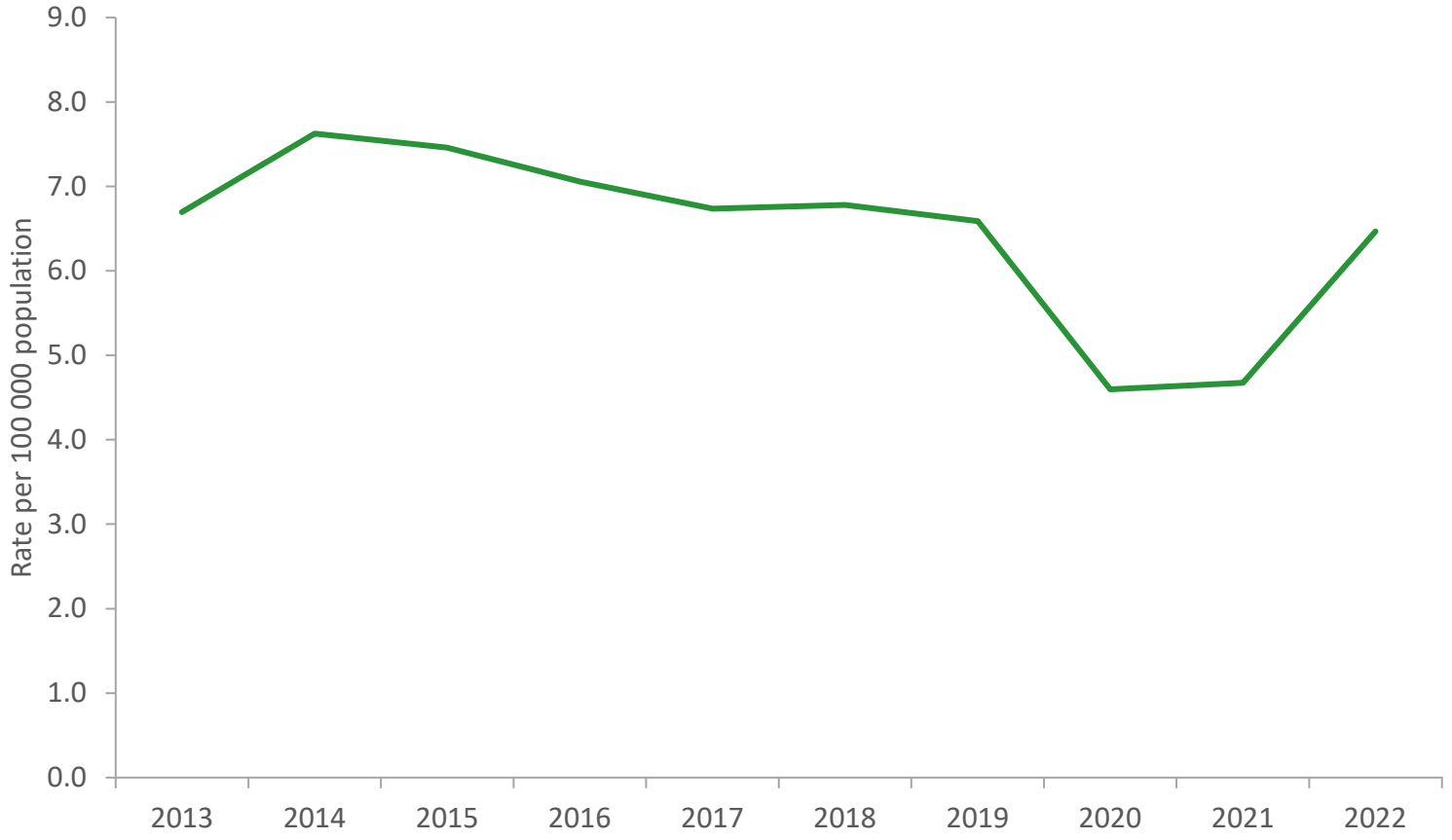


Differences between acute and chronic cases:

- More chronic cases reported than acute cases
- Chronic cases mostly older

ECDC, The European Surveillance System 2023 (unpublished).

Notification rates of hepatitis C per 100 000 population in EU/EEA countries, 2022

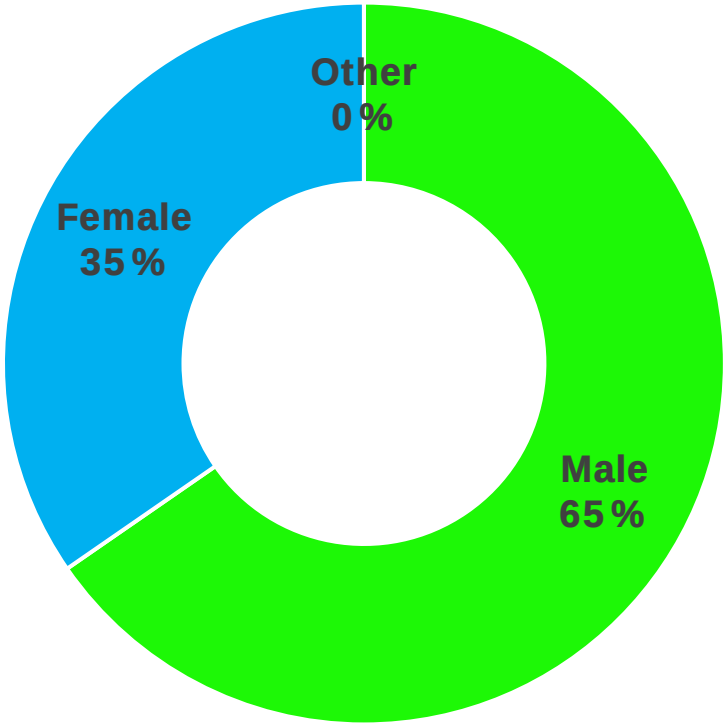


Source: Country reports from Austria, Bulgaria, Croatia, Cyprus, Czechia, Denmark, Estonia, Finland, Germany, Greece, Iceland, Ireland, Italy, Latvia, Luxembourg, Malta, Norway, Poland, Portugal, Slovakia, Slovenia, and Sweden.

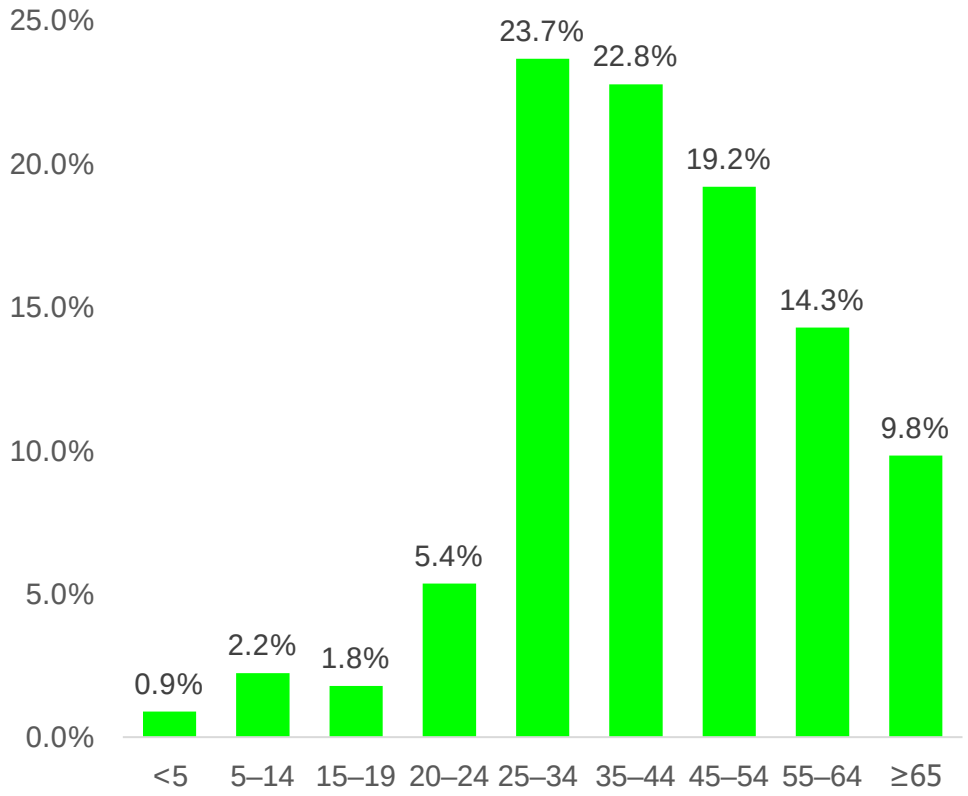
Acute hepatitis C notifications – by age and gender, EU/EEA, 2022

1 308 notified **acute cases** from 19 MS

GENDER (n=1 213)



AGE GROUPS (n=224)

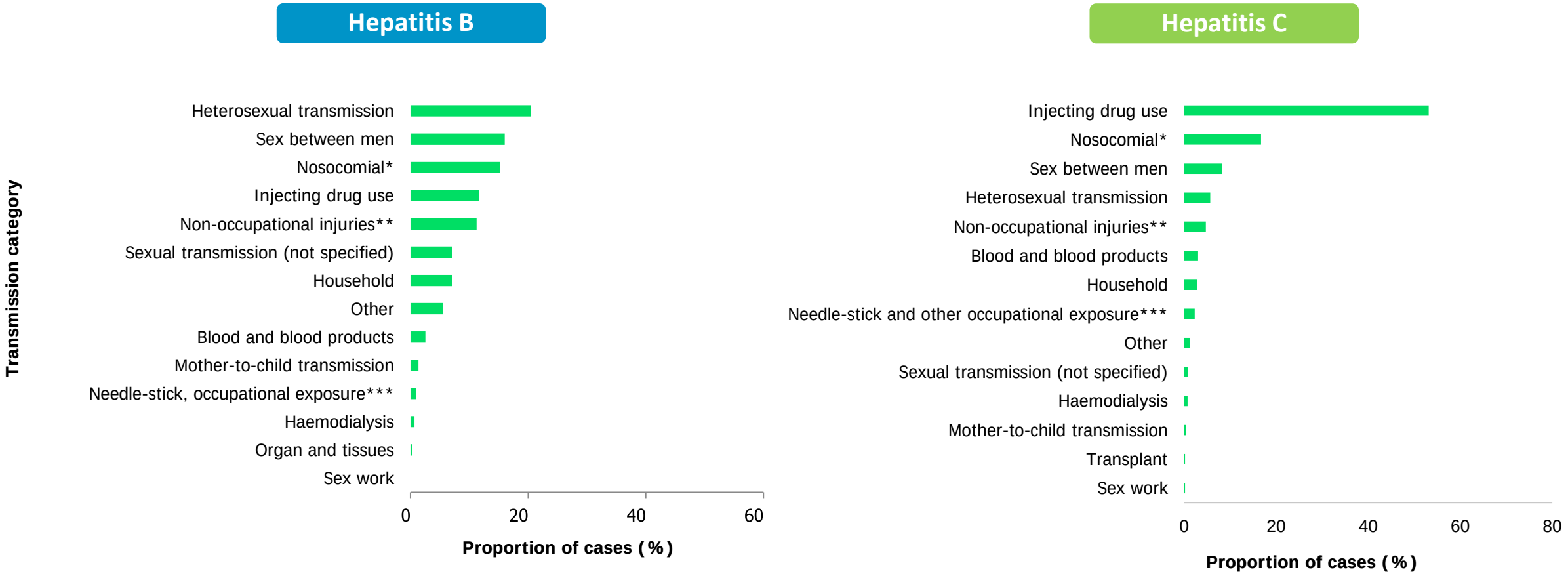


Differences between acute and chronic cases:

- More chronic cases reported than acute cases
- Chronic cases mostly older

Source: ECDC, The European Surveillance System 2023 (unpublished).

Transmission category of acute hepatitis B and C cases in EU/EEA countries, 2022

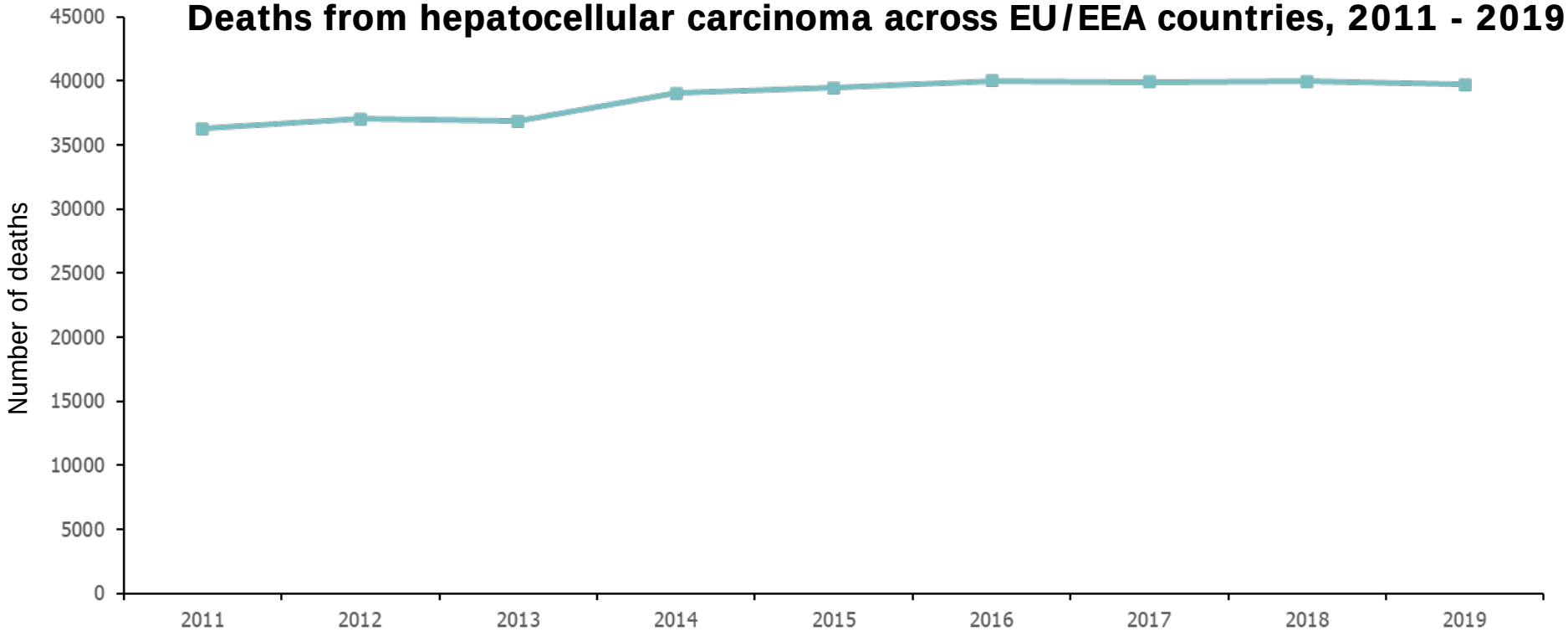


Source: ECDC, The European Surveillance System 2023 (unpublished). Reports for acute hepatitis B from Austria, Croatia, Czechia, Denmark, Estonia, Finland, Francei , Germany, Hungary, Iceland, Ireland, Italy, Latvia, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Spain and Sweden. Reports for acute hepatitis C from Austria, Croatia, Cyprus, Denmark, Estonia, Germany, Greece, Hungary, Ireland, Italy, Latvia, the Netherlands, Poland, Portugal, Romania, Slovakia, Spain, and Sweden.

*: Nosocomial transmission includes hospitals, nursing homes, psychiatric institutions, and dental services. This category refers mainly to patients exposed through healthcare settings, distinct from 'needle-stick and other occupational exposure', which refers to staff.

**: 'Non-occupational injuries' include needle sticks that occur outside a healthcare setting, bites, tattoos, piercings.

Mortality due to viral hepatitis B and C in the EU/EEA over time



Hepatitis specific mortality estimated to be 64,000 in 2015 for EU/EEA countries and the UK

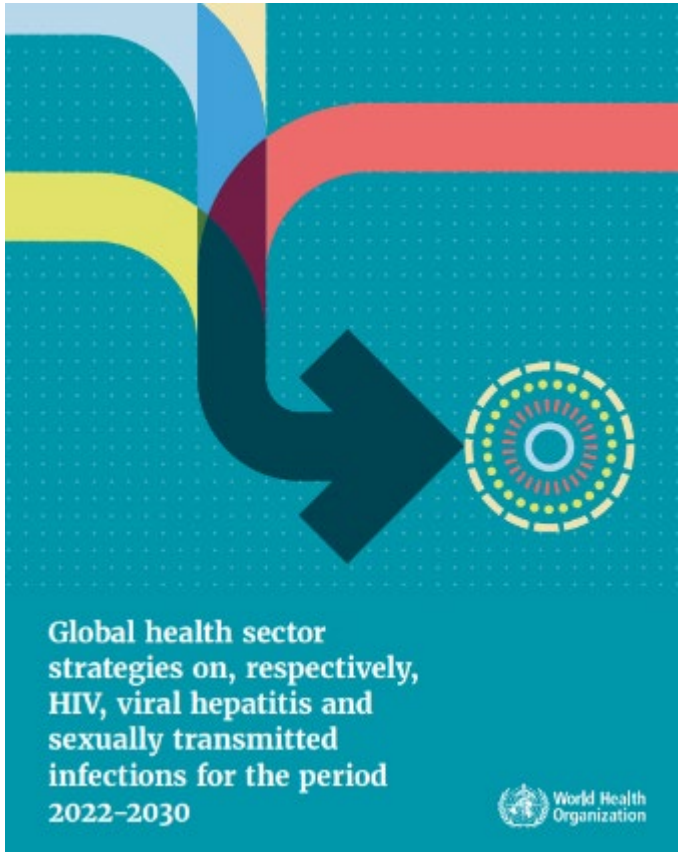
Source: Eurostat, 2022.

No significant decrease in total mortality from liver cancer and chronic liver diseases at EU/EEA level

Mortality from **hepatocellular carcinoma** continues to **increase**

Global health sector strategies on HIV, viral hepatitis and STIs for 2022-2030; WHO Europe Regional action plan 2022-2030

- “End viral hepatitis as a major public health threat by 2030”



World Health Organization
European Region

Regional Committee for Europe
72nd session

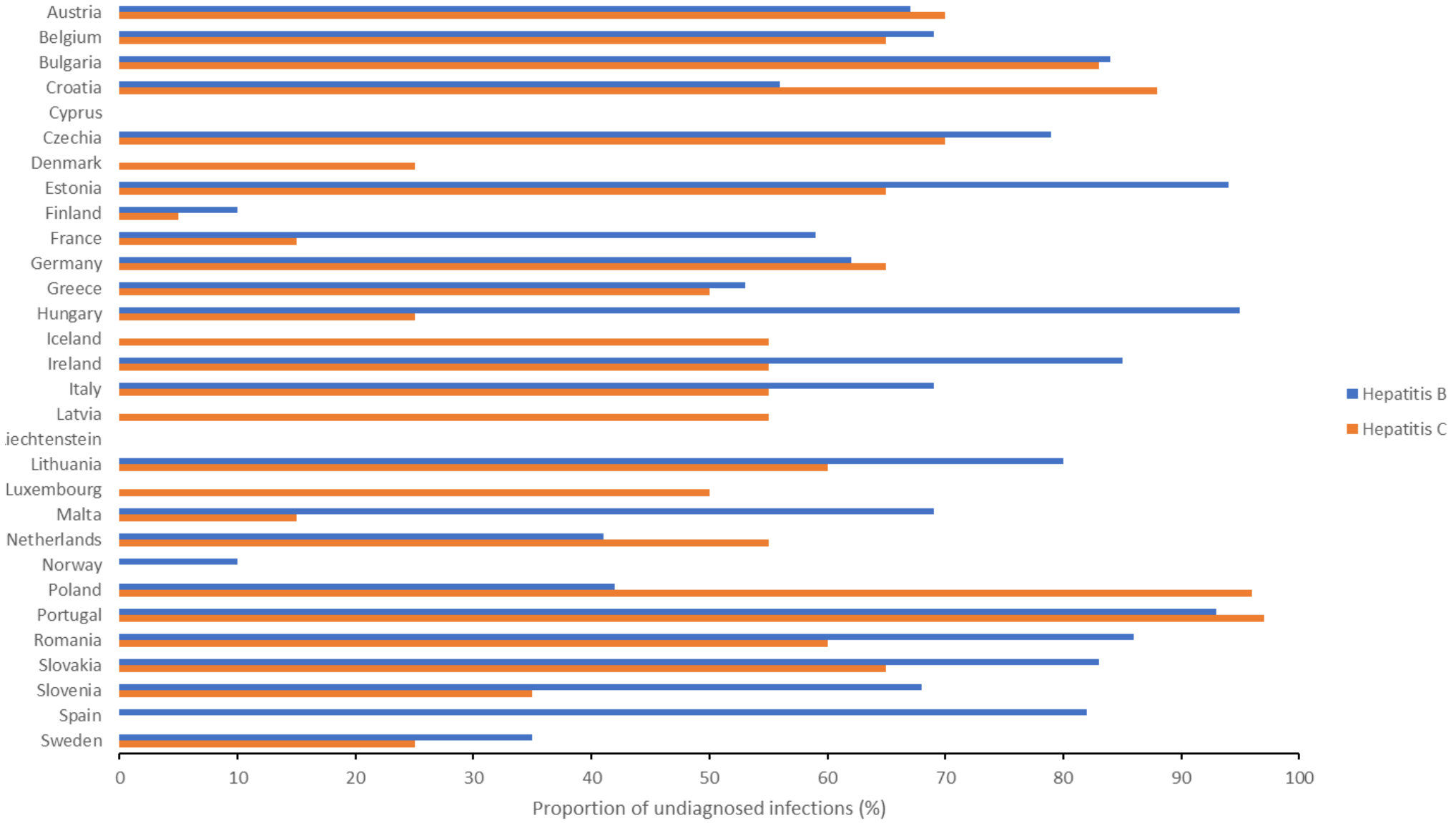
Tel Aviv, Israel, 12–14 September 2022

EUR/RC72/9 | 11 August 2022 | 220605 | ORIGINAL: ENGLISH
Provisional agenda item 7

Regional action plans for ending AIDS and the epidemics of viral hepatitis and sexually transmitted infections 2022–2030

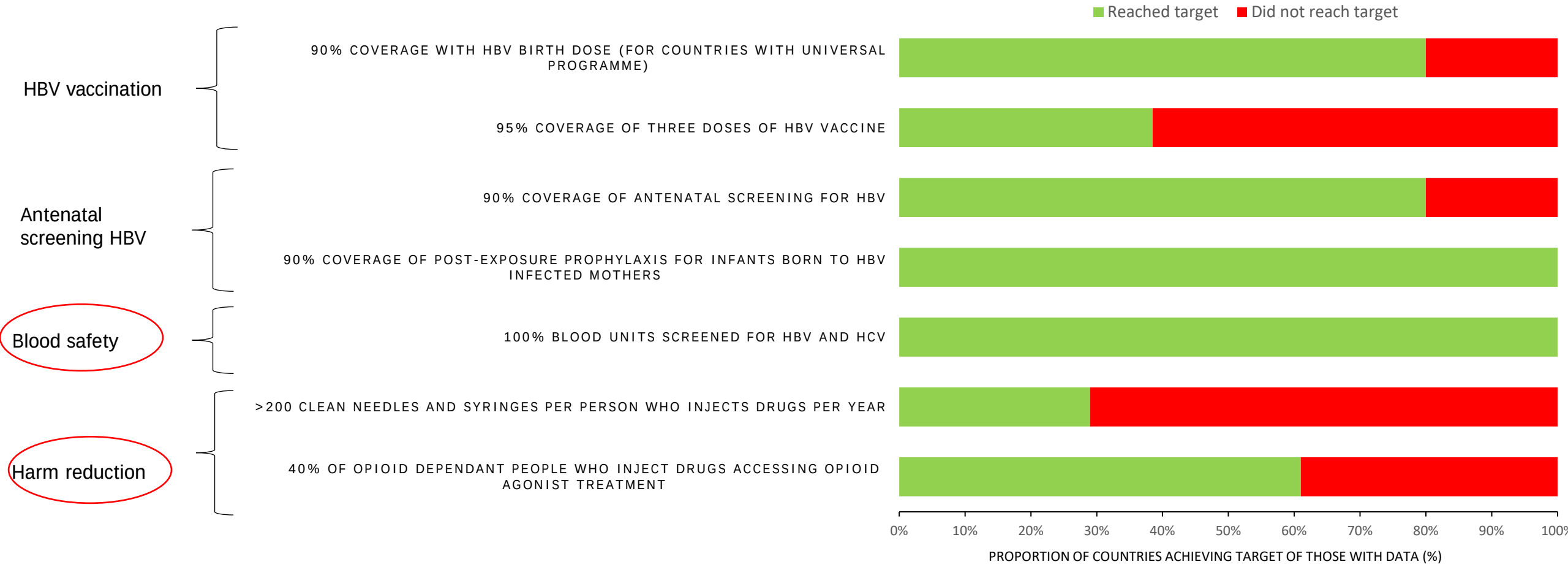
Source: https://apps.who.int/iris/rest/bitstreams/1451670/retrieve; https://apps.who.int/iris/bitstream/handle/10665/361524/72wd09e-AIDS-Hepatitis-220605.pdf?sequence=1&isAllowed=y

Estimated proportion of undiagnosed people living with viral hepatitis B and C



Source: The Polaris Observatory Collaborators. https://doi.org/10.1016/ S2468-1253(23)00233-9

Progress towards the WHO elimination targets for prevention across the EU/EEA countries, 2022



Source: European Centre for Disease Prevention and Control. Evidence brief: Prevention of Hepatitis B and C in the EU/EEA. Stockholm: ECDC; 2024.

Conclusion

- **No data source provides a complete overview of the situation in the EU/EEA**:
  - Epidemiological data to be understood considering monitoring data and vice-versa
  - Triangulation of several data sources

- **High disease burden for hepatitis B and C in EU/EEA despite a declining incidence :**
  - Large estimates of prevalences and proportions of undiagnosed infections
  - Large geographic variation
  - Key populations (migrants, IDU...) disproportionately affected
  - Increasing mortality

- **Many progress towards 2030 elimination goals but:**
  - **Many countries are far from the elimination targets**
  - **Need to upscale the prevention and control interventions targeting vulnerable populations and areas**

Acknowledgements

Austria: Ziad El-Khatib; Irene Kászoni-Rückerl; Sigrid Kiermayr; Anna Nagel; Maria Paulke-Korinek; Elise Schabus; Irrene Schmuttere; Margit, Winterleitner. Belgium: Benoit Kabamba; Sofieke Klamer; Els Plettinckx; Vanessa Suin; Dominique van Beckhoven; Thomas Vanwolleghem. Bulgaria: Mariya Tyufekchieva; Tonka Varleva. Croatia: Maja Ilic; Tatjana Nemeth-Blažić, Adriana Vince. Cyprus: Fani Theophanous. Czechia: Jitka Cástková; Vratislav,Nemecek. Denmark: Peer Brehm Christensen; Susan Cowan; Martine Grosos Aabye; Anne Øvrehus. Estonia: Jevgenia Epštein; Kristi Rüütel. Finland: Henrikki Brummer; Kirsi Liitsola; Henna Rautiainen; Päivi Viitanen. France: Cécile Brouard; Mathias Bruyand; Florcence Lot; Joisane Pillonel. Germany: Sandra Dudavera; Gyde Steffen; Ruth Zimmermann. Greece: Stergios Georgoulas; Georgia Nikolopoulou; George Papatheodoridis; Ioanna Samiou; Panagiota Touloumi ; Sois Zoutsos. Hungary: Agnes Danielisz; Maria Dudas; Emese Kozma; Zsuzsanna Molnár. Iceland: Guðrún Aspelund; Már Kristjánsson. Ireland: Jeff Connell; Suzanne Cotter; Cillian De Gascun; Joanne Moran; Aiden McCormick; Niamh Murphy; Aisling O'Leary; Mary O'Riordan. Italy: Loreta Kondili; Francesco Maraglino; Barbara Suligoi; Maria Elena Tosti; Sabrina Valle. Latvia: Inga Ažiņa; Raina Nikiforova; Serges Nikisins. Liechtenstein: Silvia Dehler; Esther Walser-Domjan. Lithuania: Brigita Kairiene. Luxembourg: Carole Devaux. Malta: Jackie Melillo; Tanya Melillo. Netherlands: Silke David; Jaap Maas; Annemarie Meiberg; Eline Op de Coul; Marleen van Dijk; Irene Veldhuijzen. Norway: Hilde Kløvstad. Poland: Robert Flisiak; Małgorzata Stępień; Karolina Zakrzewska. Portugal: Joana Bettencourt; Rui Tato Marinho; Sofia Ribeiro. Romania: Odette Popovici; Corina Silvia Pop. Slovakia: Mária Avdicová. Slovenia: Marta Grgič-Vitek; Jože Hren; Irena Klavs; Janja Križman Miklavčič; Eva Leban; Mojca Matičič; Mario Poljak; Urška Rahne Potokar. Spain: Agustín Albillos; Maria Buti; Javier Crespo; Julia del Amo; Asunción Diaz; José Luis Calleja; Javier García-Samaniego; Victoria Hernando; Oriana Ramírez-Rubio; Pablo Ryan. Sweden: Soo Aleman; Maria Axelsson; Hanna Edberg; Josefine Lundberg Ederth; Martin Kåberg. European Liver Patients' Association: Marko Korenjak. European Monitoring Centre for Drugs and Drug Addiction: Thomas Seyler. WHO Regional Office for Europe: Marcelo Naveira, Giorgi Kuchukhidze. EMIS: Axel J Schmidt. Correlation Network: Rafaela Rigoni, Tammi Tuukka. Viral Hepatitis Prevention Board: Greet Hendrickx. European Association for the Study of the Liver: Maria Buti. National AIDS Trust: Katherine Turpie. World Hepatitis Alliance: Rachel Halford, Cary James.

Thank you!

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Du don à la vie

ecdc
EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL

SOHO-NET ORGANS MEETING

Sharing of French experience with hepatitis C positive donors and with early and large access to DAAs treatment

—Dr C. Antoine, Dr Camille Legeai, Dr Sophie Lucas Samuel, Pr F. Kerbaul, Pr Michel Tsimaratos—

www.agence-biomedecine.fr

French context about HCV infection

1. Scandal over tainted blood in France "national traumatism"

- Distribution of contaminated blood stocks until 1985 to patients, leading to an outbreak of HIV/AIDS and hepatitis C

2. Donor serologic and nucleic acid amplification testing (NAT) : mandatory by law

- Triplex assay allowing NAT results for HIV, HBV, and HCV on organ donors are mandatory since 2010
- In an exhaustive manner available before organ allocation since 2021
- Procurement and organ transplantation have been authorized, as an exception, according to a national protocol specified by law **since 2006**

3. In 2013, France was one of the first countries to market the new direct antiviral agents to treat chronic hepatitis C

- Covered by the French Health Insurance System
- Multidisciplinary committee had to validate the best timing and treatment option to allow drugs delivery

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HCV liver disease in France

Before 2013 : 24-26% of patients were listed for LT due to HCV liver disease

- 55-60 % of them have decompensated cirrhosis, 10-12% for retransplant

The 2th-generation of DAAs = progress in the therapeutic management of patients with HCV

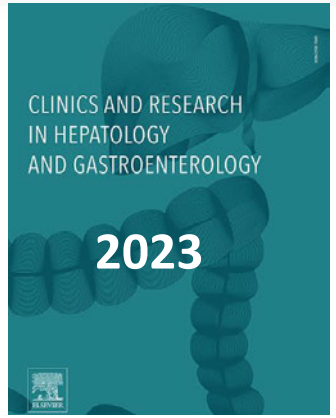
- Sustained virological response.
- Extent use of DAAs for both liver transplant candidates and recipients
  - To eradicate HCV
  - To avoid liver decompensation

    Belli et al, Journal of hepatology, 2016
  - To prevent and to treat HCV-reinfection of the graft
  - To improve transplant results

Original article

Impact of direct antiviral agents for hepatitis C virus -induced liver diseases on registration, waiting list and liver transplant activity in France

Audrey Coilly [a,*], Carine Jasseron [b], Camille Legeai [b], Filomena Conti [c], Christophe Duvoux [d], Nassim Kamar [e], Sébastien Dharancy [f], Corinne Antoine [b,*], collaborators [1]

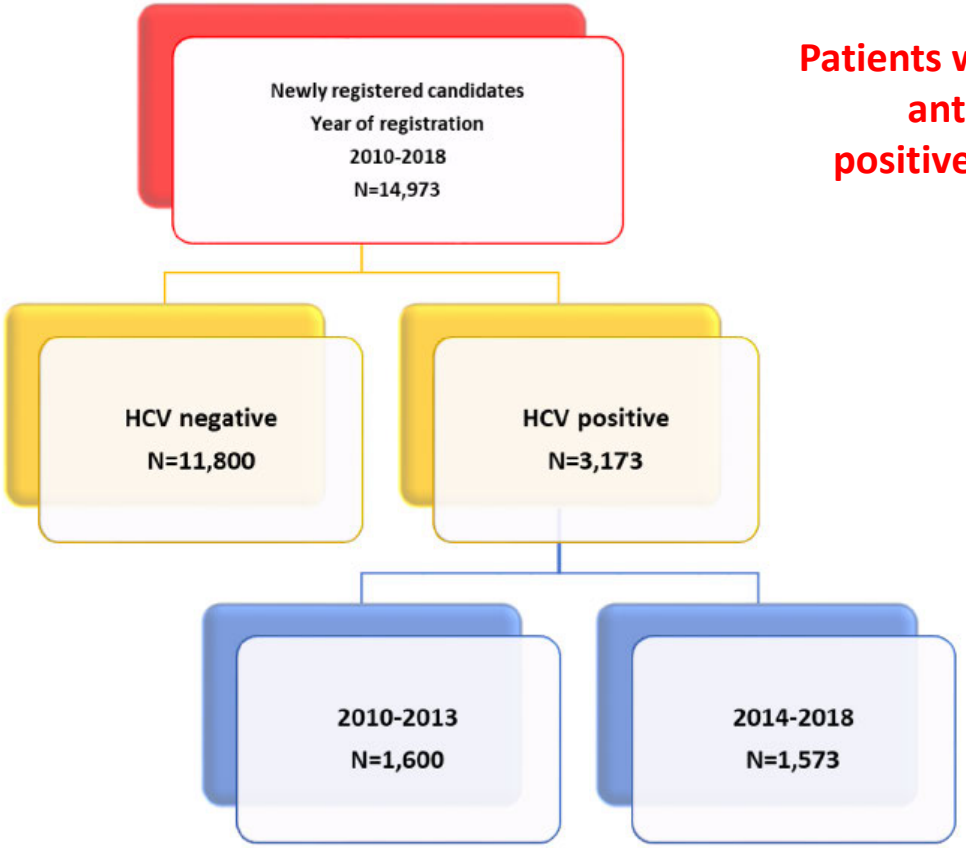


Study objectives

Impact of the 2th-generation of DAAs on registration and outcome on the WL for LT

Impact of the 2th-generation of DAAs on transplant results

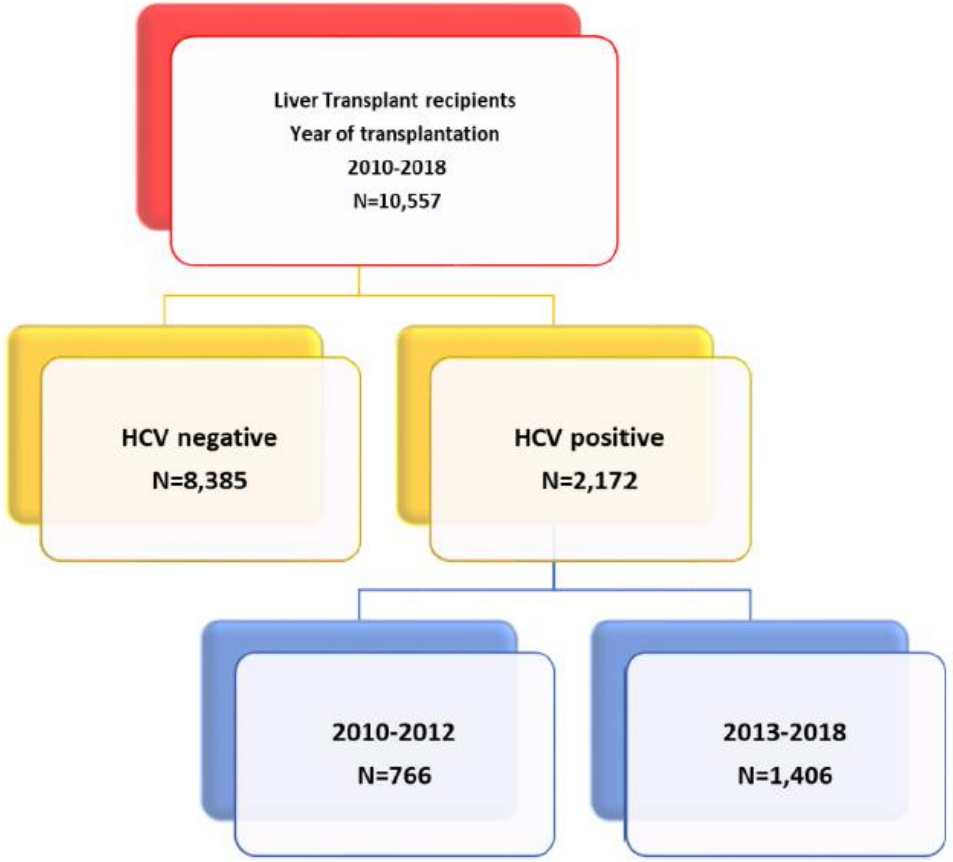
A. Candidates on the waiting list



Patients with positive HCV antibodies +/- positive HCV viral load

Newly adult registered candidates from 2010 to 2018 in France
Comparison of the 2 periods before and after DAA introduction: 2010–2013 (n = 1600) versus 2014–2018 (N = 1573).
Trends over time of 1. Registration on WL 2. Liver TR indications
3. Cumulative incidence of death and delisting for worsening conditions (Competing risk analysis)

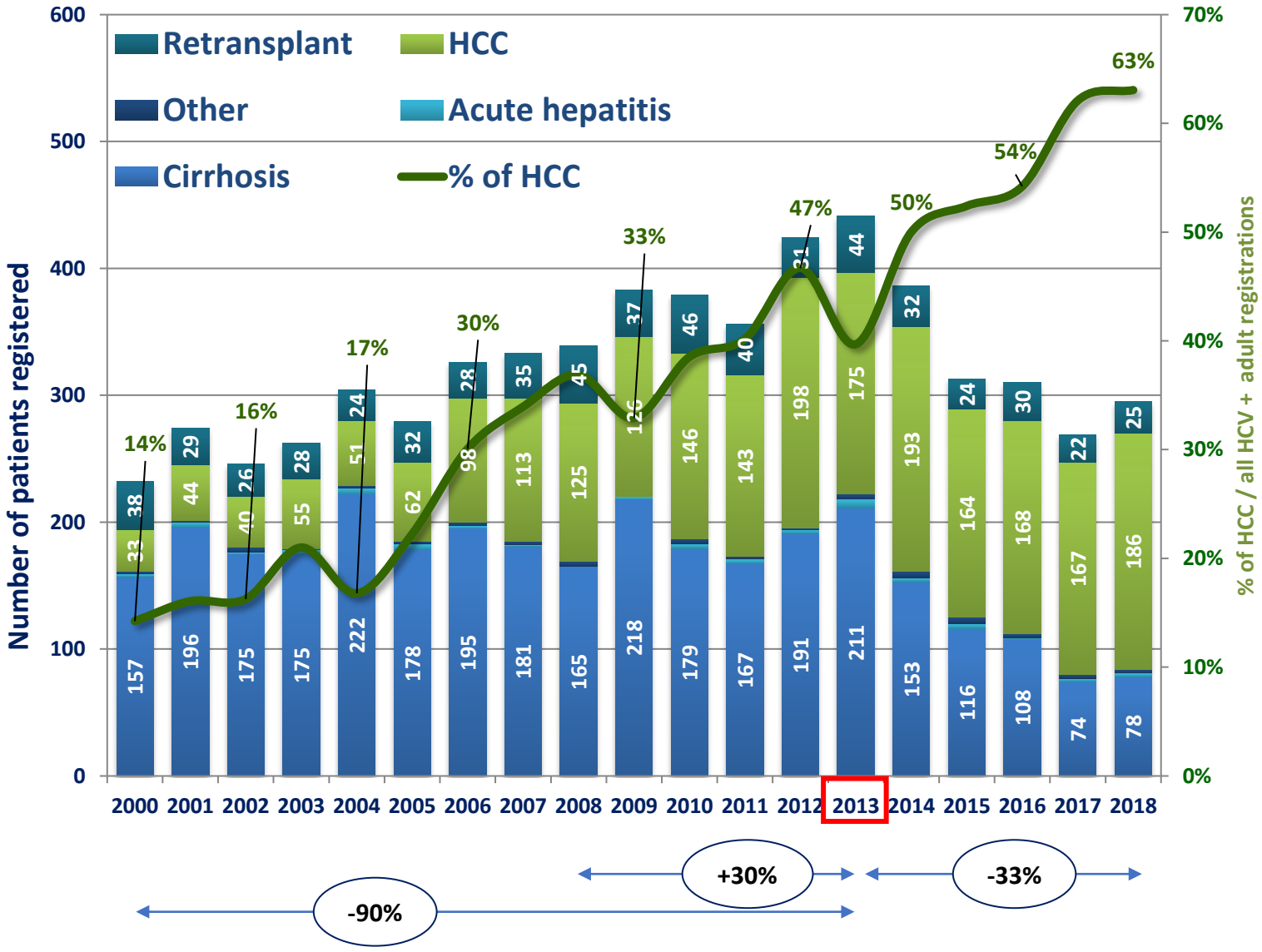
B. Liver transplant recipients



All adult patients with HCV induced liver diseases
Comparison of the 2 periods before and after DAA introduction: 2010–2012 (n = 766) versus 2013–2018 (N = 1406)
Post transplant mortality analysis
Kaplan-Meier method and the log-rank test

National database : CRISTAL

Changes in the waiting list



Incidents : new registrations for HCV-induced liver diseases

1. Candidates listed for HCV-induced liver diseases :
   - 33 % from 2013 to 2018
2. Listing for retransplantation decreased of 43% since 2013.
3. HCV-HCC : predominant indication : 21% (2003) →63% (2018)

Prevalents : candidates with HCV-induced liver diseases

4. Significant decrease of WL mortality (-65%)
5. Decrease of 42% of delisting for worsening condition from 2014 to 2018
6. Significant increase of 113% of delisting for improving condition
7. Increase in the rate of inactive patients on WL : from 26% in 2013 to 51% in 2018

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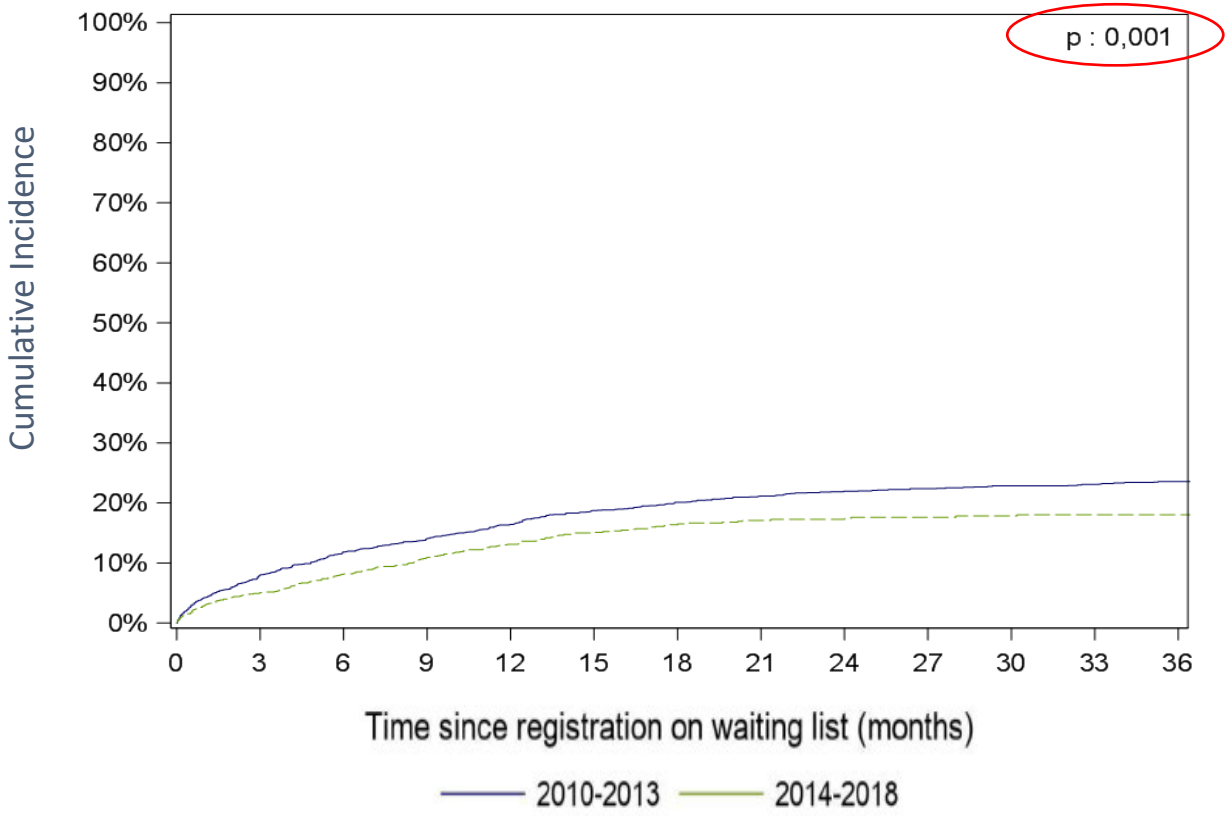
The waiting list patient survival increased

Comparison of 2 periods (2010-2013 versus 2014-2018)



Cumulative incidence of death or delisting for worsening condition on the LT waiting list taking into account the competive risk of transplantation in % [95% CI]						
Period	N	at 3 months	At 6 months	at 12 months	At 24 months	at 36 months
2010-2013	1598	8 [7-9]	12 [10-14]	16 [15-18]	22 [20-24]	24 [22-26]
2014-2018	1572	5 [4-6]	8 [7-10]	13 [11-15]	17 [15-20]	NC

Factors independently associated with death or delisting for worsening condition :

- MELD score at registration
- Period (2010- 2013) compared to (2014-2018)

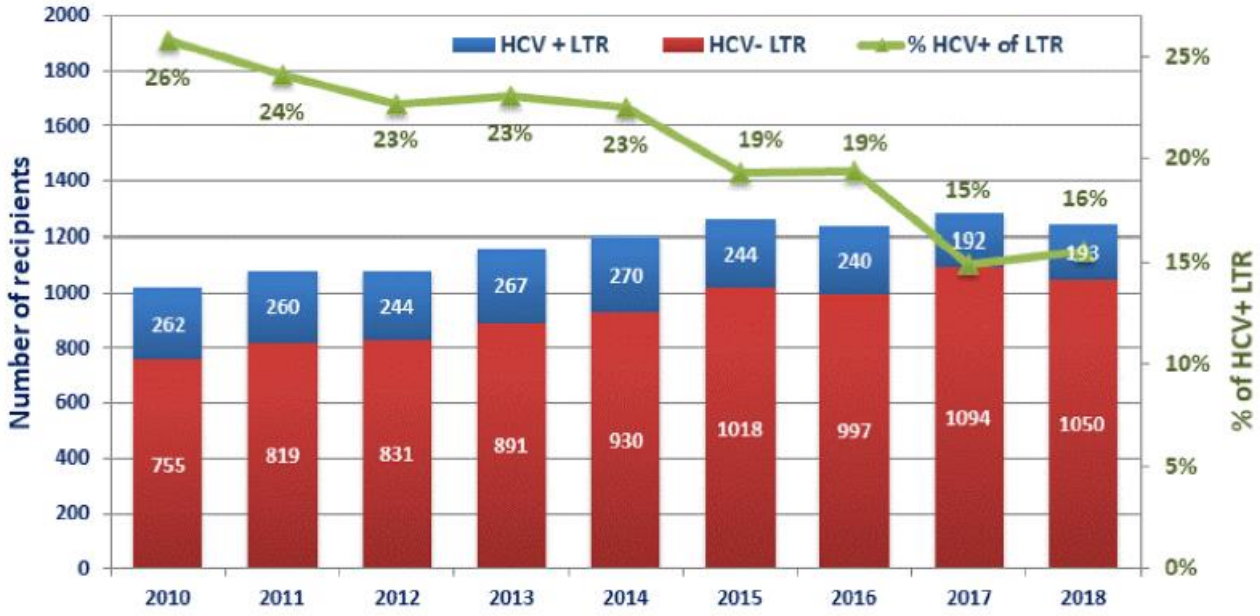
No difference in 1-y waiting list survival in non-HCV patients

Post transplant outcome

HCV-induced liver diseases

- 26% of liver transplant in 2010
- 16 % of liver transplant in 2018

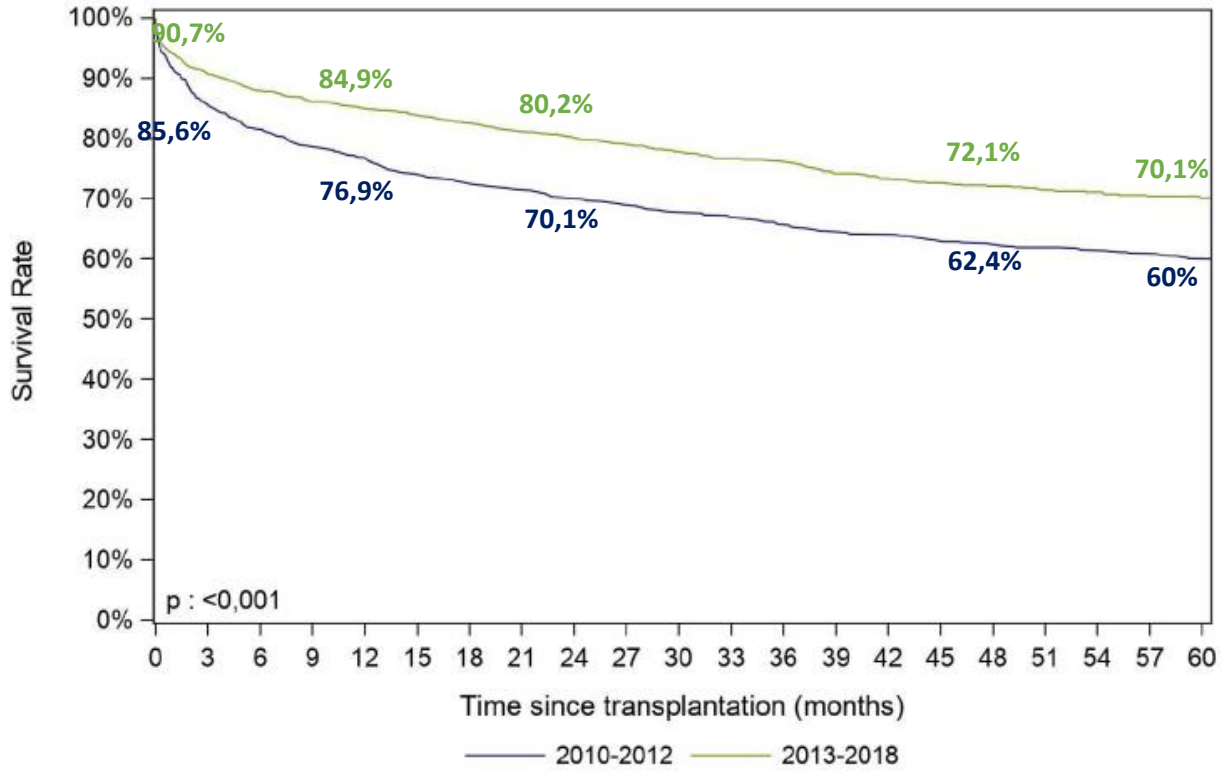
(overall LT activity : + 21,3% from 2010 to 2018)



The 1y-graft survival rate was significantly improved after the extent use of DAAs ((2010-2012) versus (2013-2018)

1 y graft survival 76,9 % → 84,9%

Remained significantly lower in 2013-2018 in a multivariate survival (cox model) adjusted on MELD at LTR, recipient and donor age and donor's etiology of death (HR=0,5 [0,4-0,6



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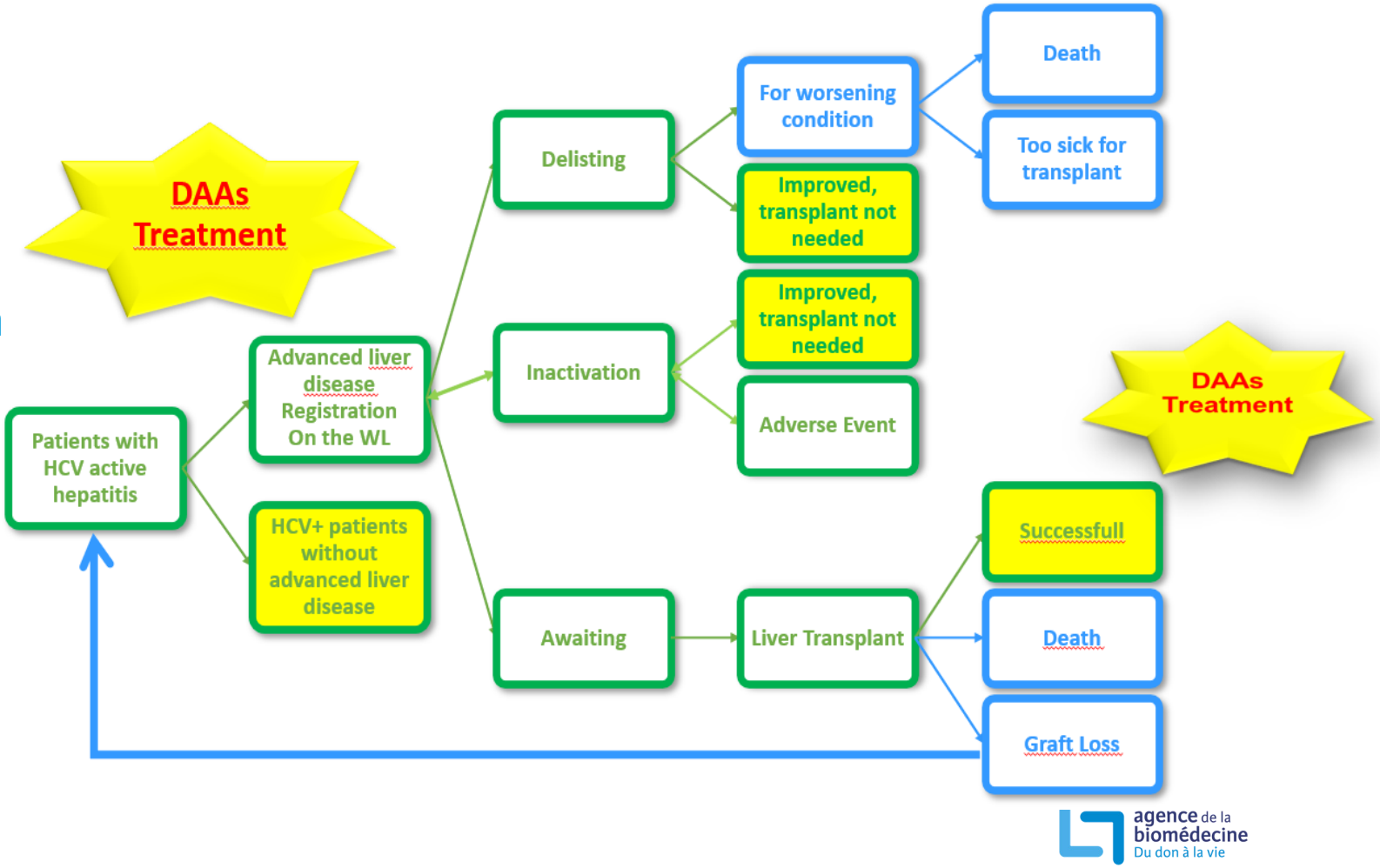
Great impact of the early and large access to DAAs treatment in France (1)

From HCV candidates and recipients perspectives

They have been benefiting from access to DAAs.

- Decrease of WL mortality and delisting for worsening condition
- Increase of delisting for improving condition
- Increase of inactive patients rate on waiting list
- With improving graft and patient survival, including less relisting for retransplantation

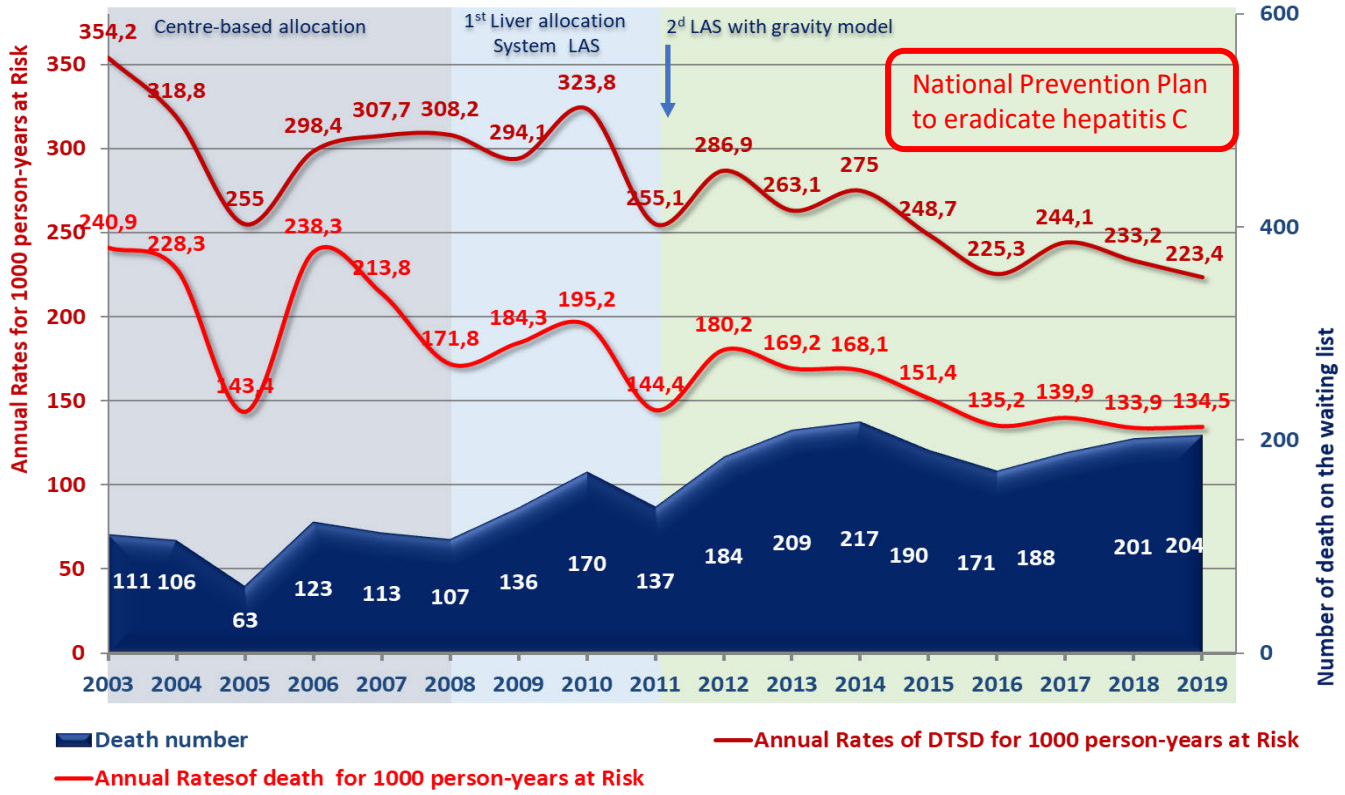


Great impact of the early and large access to DAAs treatment in France (2)

From non HCV candidates perspectives

The decrease of transplant needs for HCV liver disease

- May contribute to the decrease of overall waiting list mortality and removal for worsening conditions observed in France
- Grafts could be redistributed towards HCV negative severe liver transplant candidates
- Despite overall increase of new registrations (Total candidates + 15,8%)



Significant decrease of overall waiting list mortality and removal for worsening conditions from 2013 to 2019

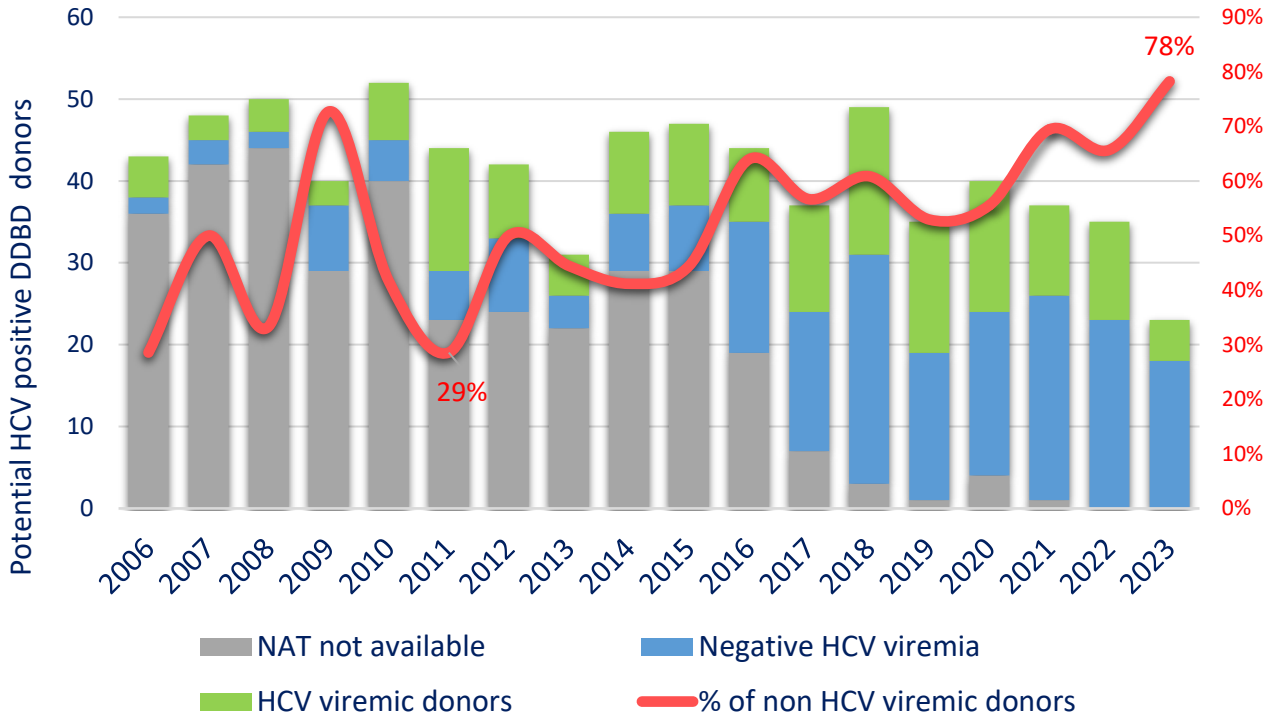
Great impact of the early and large access to DAAs treatment in France (3)

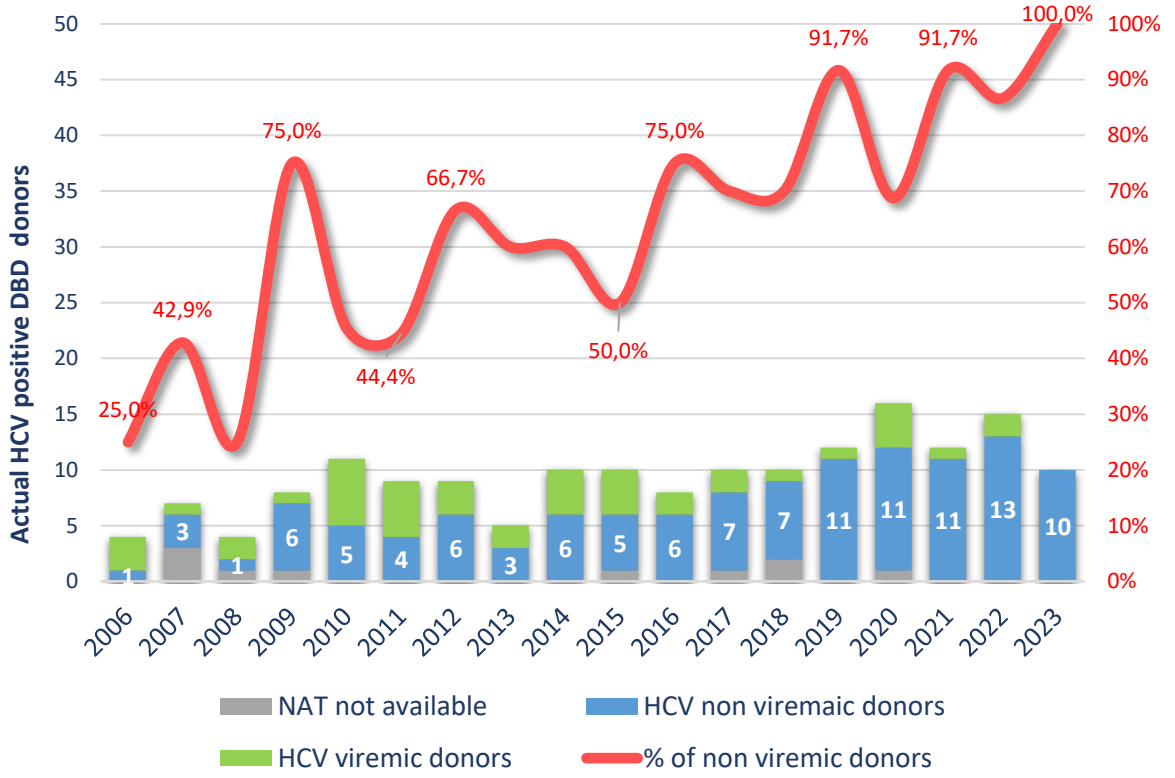
From French Health Insurance System perspectives

- Cost effective strategy : very high annual direct medical cost associated with HCV hepatic and extrahepatic manifestations → DAA treatment was projected to result in cost savings of €316 million per year. *(Cacoub et Al, J Viral Hepat 2018)*
- A reduced risk for mortality and incidence of hepatocellular carcinoma
  (French ANRS CO22 cohort Carra Lancet 2019)
- Leading to a secondary decline in HCC transplantation indications (- 20% in 5 years)

→ Decreasing number of HCV positive donors

Over time: Decrease of positive-HCV donors
Exhaustivity of Viral load assessment before organ allocation





2023 : deceased donors with positive HCV serology

- Systematic screening by NAT before organ allocation
- 78% of potential donors have a negative HCV viremia
- 100% of actual donors have a negative HVC viremia

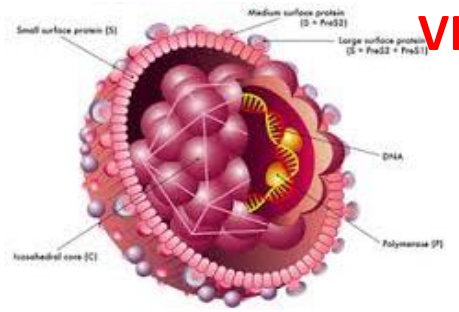
2023
16 kidney transplants (80% of utilized donors)
6 liver transplants (60% of utilized donors)

Legal framework for HCV positive donors : derogatory exception

26 décembre 2015 JOURNAL OFFICIEL DE LA RÉPUBLIQUE FRANÇAISE Texte 71 sur 247

Décrets, arrêtés, circulaires

Arrêté du 23 décembre 2015 complétant l'arrêté du 23 décembre 2010 modifié pris en application des articles R. 1211-14, R. 1211-15, R. 1211-16, R. 1211-21 et R. 1211-22 du code de la santé publique



Donor risk assessment

HCV Antibodies

Viral load (nucleic acid amplification test positive)

- Positive or not available
- Negative

Only if the Fibrosis scoring is less than F2

- Liver biopsy
- Non invasive methods for assessing liver fibrosis

Traced in CRISTAL Donor Registry

Recipient profile

HCV antibodies

Viral load (nucleic acid amplification test positive)

- If not available, considered as negative
- Date of the last viral load assessment

Informed and consent

Traced in CRISTAL Recipient Registry

If patient's prognosis is life-threatening and the therapeutic alternatives become inappropriate,

- «so that waiting for a graft other than the one proposed in this derogation exception is detrimental to the recipient's survival».

agence de la biomédecine
Du don à la vie

Derogatory exception according to viral profile

Deceased donors
Positive HCV Antibodies
Liver: fibrosis score < F2

Positive HCV viral load

HCV-viremic donor
At the time of graft offer
For recipients with :
- Positive HCV Antibodies
- Positive HCV viral load
- Informed and consent

Negative HCV viral load

Non HCV-viremic donor
At the time of graft offer
For recipients with :
- Positive HCV Antibodies
- Positive or negative HCV viral load
- Informed and consent

Living donors
Positive HCV Antibodies
Negative HCV viral load

consent to the disclosure to the recipient of medical information concerning his/her immune status with regard to viral infection

Experts assessment
Metavir Scoring < F2 (Non invasive Methods for Assessing Liver Fibrosis)

Negative viral load > 3 months
after complete treatment or documented spontaneous viral eradication

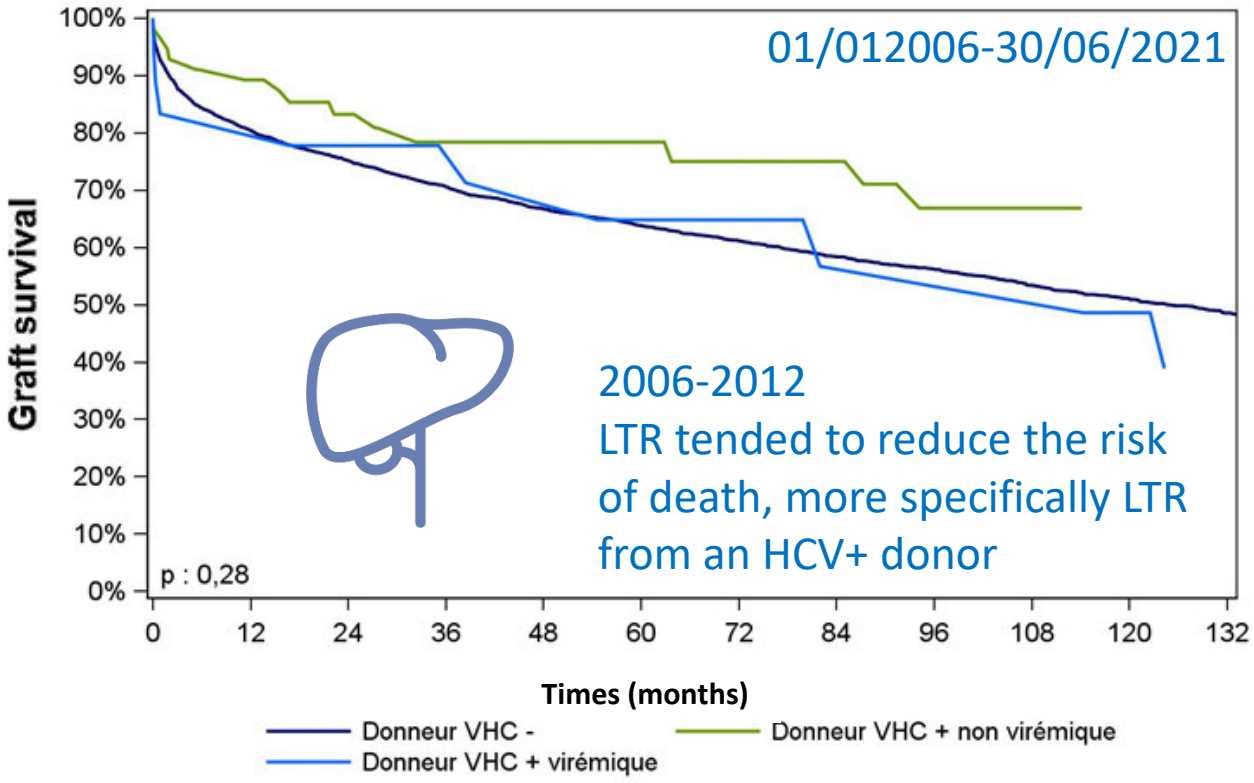
Non HCV-viremic living donor
For recipients with :
- Positive or negative HCV Antibodies
- Whatever HCV viral load
- Informed and consent

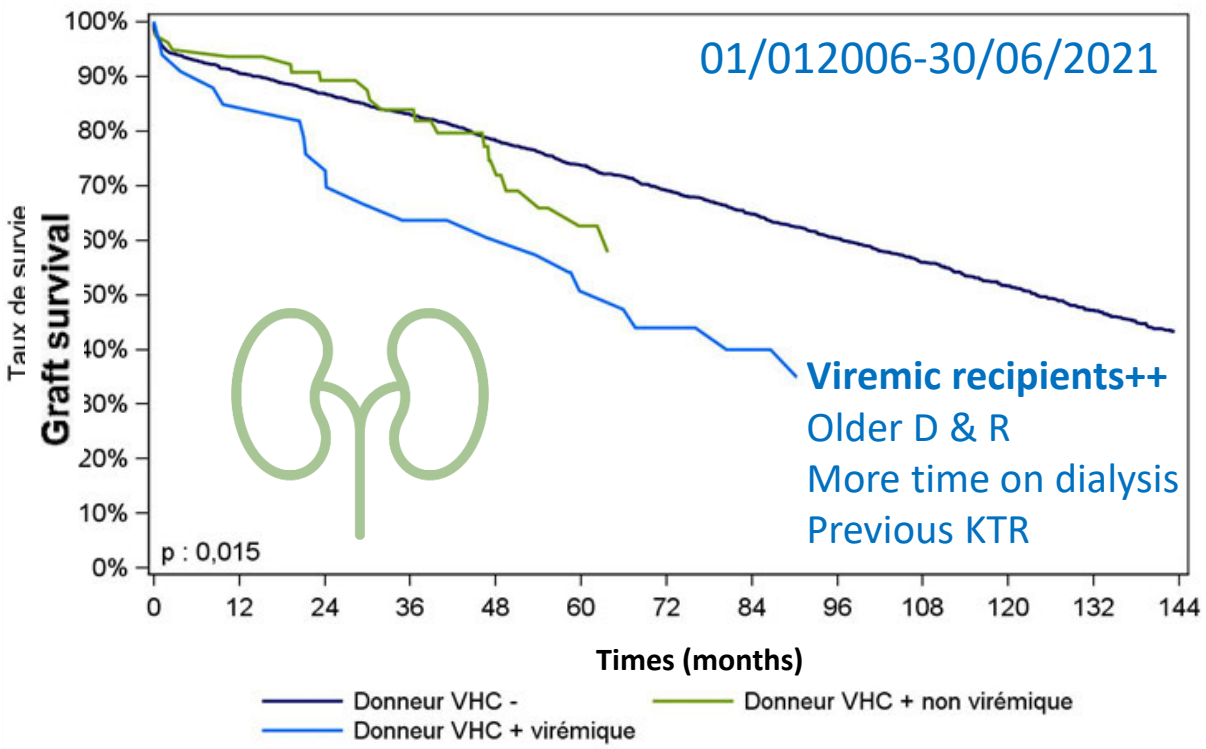
Negative viral load known to be negative < 3 months

Recent non HCV-viremic living donor
For recipients with :
- Positive HCV Antibodies
- Whatever HCV viral load
- Informed and consent

agence de la biomédecine
Du don à la vie

Graft survival according to donor HCV serology and viremia in HCV positive recipients





Donor HCV status and viremia	N	1-year survival	3-years survival	5-years survival	10-years survival	Median (months)
Negative HCV donor	3507	80,5% [79,2% - 81,8%]	70,6% [69,0% - 72,1%]	63,8% [62,2% - 65,4%]	51,0% [49,1% - 52,9%]	124,6 [114,4 - 135,6]
Positive HCV non-viremic donor	56	89,2% [77,6% - 95,0%]	78,4% [64,1% - 87,5%]	78,4% [64,1% - 87,5%]	NO	NO
HCV-viremic donor	18	83,3% [56,8% - 94,3%]	77,8% [51,1% - 91,0%]	64,8% [37,5% - 82,5%]	48,6% [22,0% - 70,9%]	114,3 [38,4 - .]

Donor HCV status and viremia	N	1-year survival	3-years survival	5-years survival	10-years survival	Median (months)
Negative HCV donor	2020	90,6% [89,3% - 91,8%]	83,0% [81,3% - 84,6%]	73,7% [71,6% - 75,7%]	51,6% [49,0% - 54,2%]	123,9 [116,5 - 130,8]
Positive HCV non-viremic donor	78	93,6% [85,3% - 97,3%]	83,9% [72,6% - 90,8%]	62,6% [46,2% - 75,2%]	NO	NO
HCV-viremic donor	33	84,8% [67,4% - 93,4%]	63,6% [44,9% - 77,5%]	50,7% [32,6% - 66,3%]	NO	65,9 [29,3 - 98,8]

Lower graft survival in viremic recipents before DAA introduction

agence de la biomédecine
Du don à la vie

Regulatory developments expected

Deceased donors
Positive HCV Antibodies
~~**Liver: fibrosis score < F2**~~

positive HCV viral load

HCV-viremic donor
At the time of graft offer
For recipients with :
- Positive HCV Antibodies
- Positive HCV viral load
- Informed and consent

Negative HCV viral load

Non HCV-viremic donor
At the time of graft offer
For recipients with :
- Positive or **negative** HCV Antibodies
- Positive or negative HCV viral load
- Informed and consent

Living donors
Positive HCV Antibodies

consent to the disclosure to the recipient of medical information concerning his/her immune status with regard to viral infection

Experts assessment
Metavir Scoring < F2 (Noninvasive Methods for Assessing Liver Fibrosis)

Negative viral load >3 months
after complete treatment or documented spontaneous viral eradication

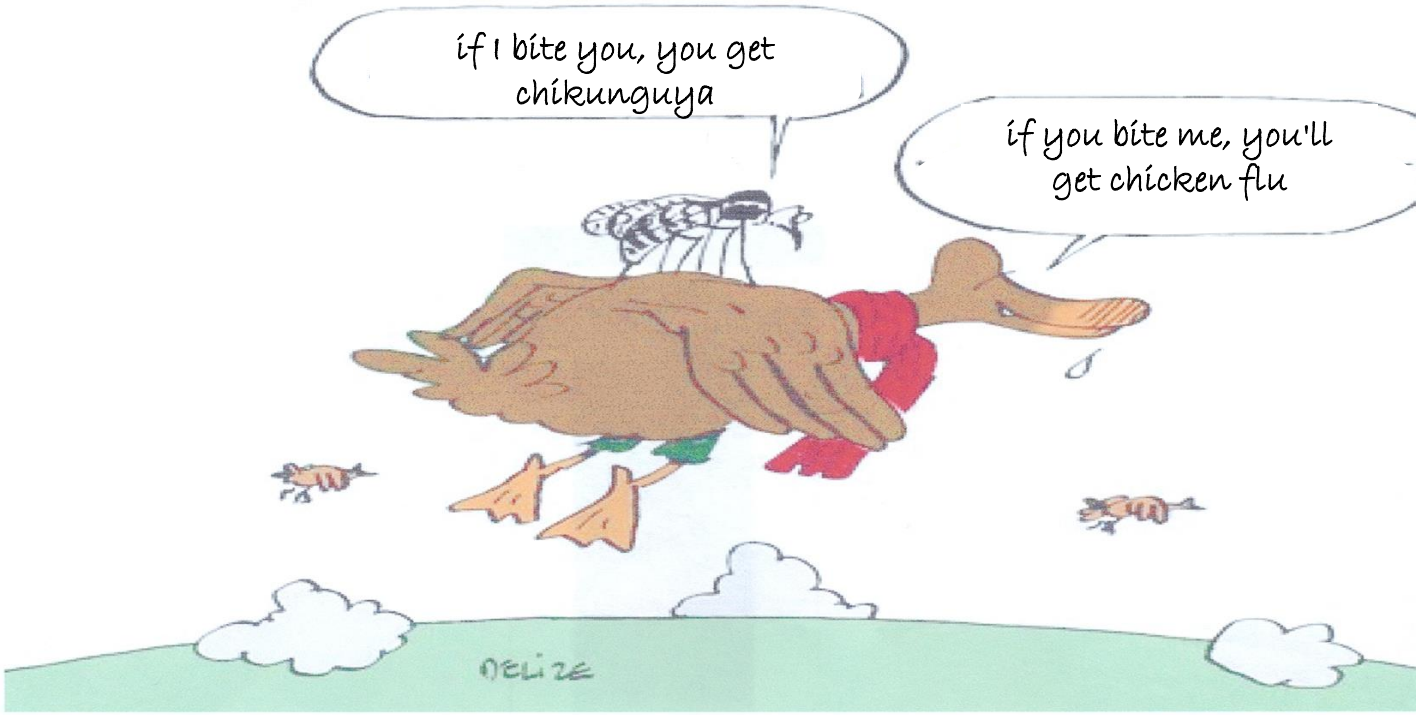
For recipients with :
- Positive or negative HCV Antibodies
- Whatever HCV viral load
- Informed and consent

Negative viral load known to be negative < 3 months

For recipients with :
- Positive HCV Antibodies
- Whatever HCV viral load
- Informed and consent

Any cases of HCV transmission from seropositive, nonviremic donors in 15 years

It's all a question of benefit/risk balance…

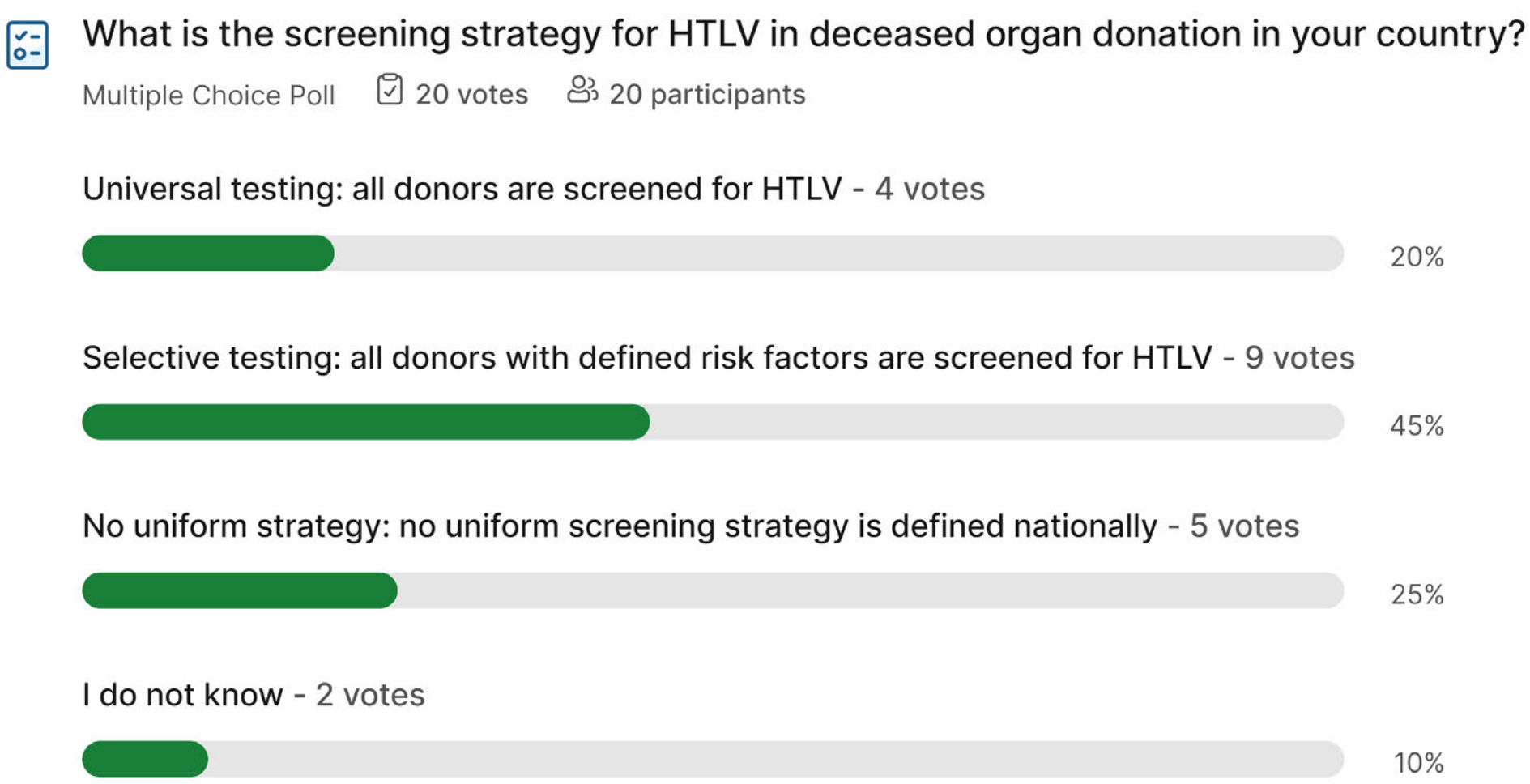


Session 5
Screening of donors for HTLV-1
18 June

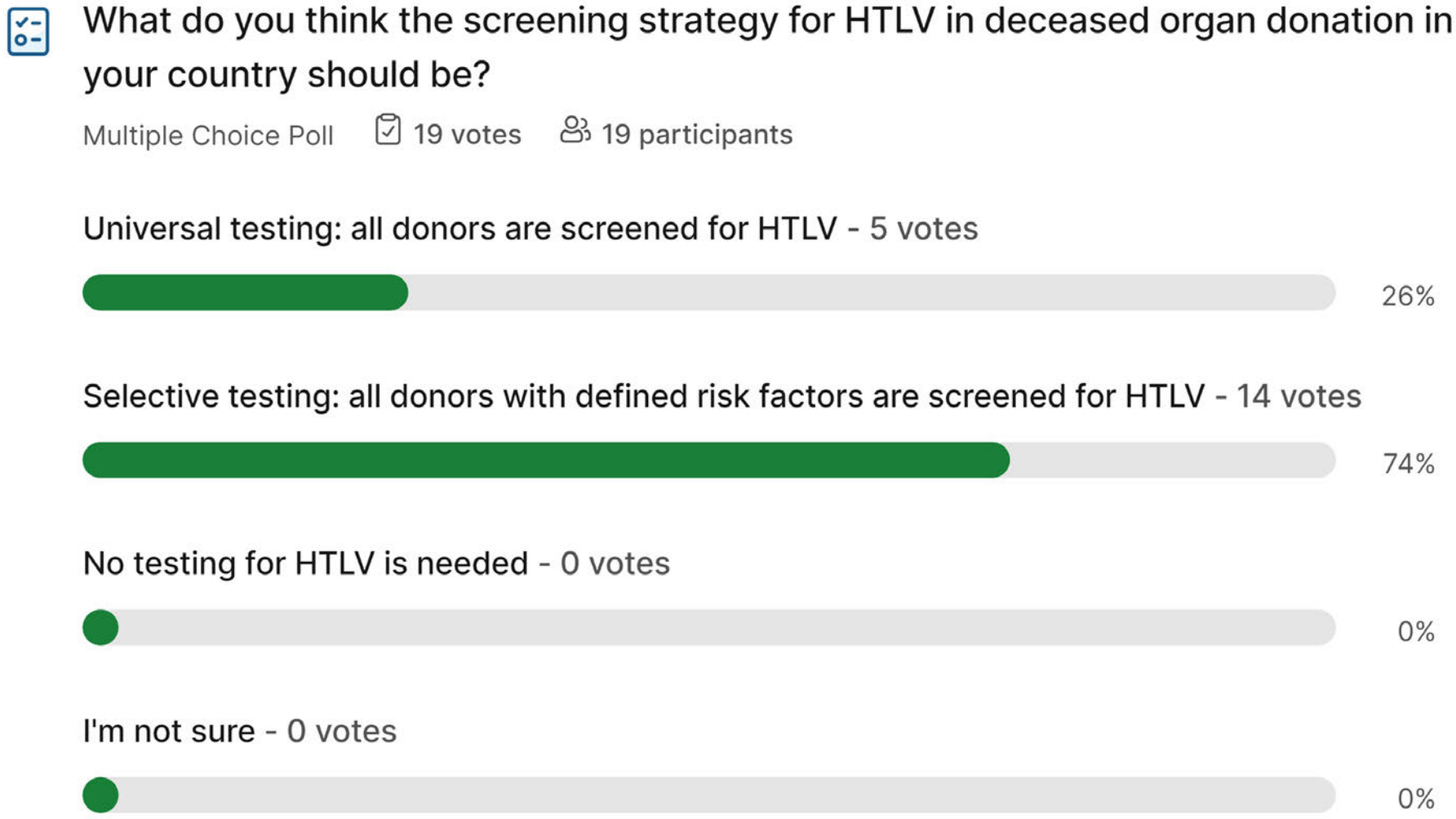
Session overview

1. **Epidemiological overview of HTLV-1** – Antoine Gessain, Institut Pasteur, France
2. **Testing of organ donors for HTLV-1 in Spain** – Beatriz Mahillo Durán, NFP Spain
3. **Strategies for testing organ donors for HTLV-1 in Romania** – Guenadiy Roumenov Vatachki, National Transplant Agency, Romania
4. **Discussion on strategies for testing of organ donors for HTLV-1 in EU/EEA** – All

But first... a couple of questions



But first... a couple of questions



Global Epidemiological Aspects of HTLV-1 in the World

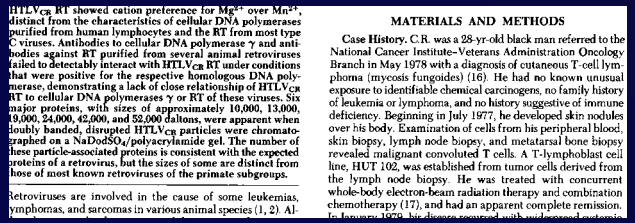
Antoine Gessain/Olivier Cassar

Unité d'Epidémiologie et Physiopathologie des Virus Oncogènes

Institut Pasteur, CNRS UMR 3659

Primate T Lymphotropic Viruses: Four Types

HTLV-1/STLV-1

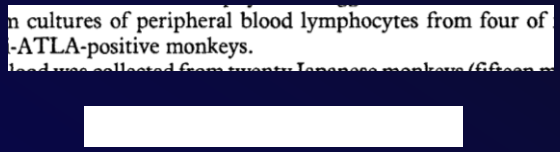


HTLV$_{CR}$ RT showed cation preference for Mg^{2+} over Mn^{2+}, distinct from the characteristics of cellular DNA polymerases purified from human lymphocytes and the RT from most type C viruses. Antibodies to cellular DNA polymerase γ and antibodies against RT purified from several animal retroviruses failed to detectably interact with HTLV$_{CR}$ RT under conditions that were positive for the respective homologous DNA polymerase, demonstrating a lack of close relationship of HTLV$_{CR}$ RT to cellular DNA polymerases γ or RT of these viruses. Six major proteins, with sizes of approximately 10,000, 13,000, 19,000, 24,000, 42,000, and 52,000 daltons, were apparent when doubly banded, disrupted HTLV$_{CR}$ particles were chromatographed on a $NaDodSO_4$/polyacrylamide gel. The number of these particle-associated proteins is consistent with the expected proteins of a retrovirus, but the sizes of some are distinct from those of most known retroviruses of the primate subgroups.

Retroviruses are involved in the cause of some leukemias, lymphomas, and sarcomas in various animal species (1, 2). Al-

MATERIALS AND METHODS

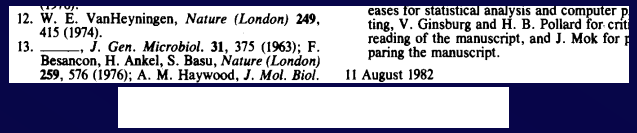
Case History. C.R. was a 28-yr-old black man referred to the National Cancer Institute–Veterans Administration Oncology Branch in May 1978 with a diagnosis of cutaneous T-cell lymphoma (mycosis fungoides) (16). He had no known unusual exposure to identifiable chemical carcinogens, no family history of leukemia or lymphoma, and no history suggestive of immune deficiency. Beginning in July 1977, he developed skin nodules over his body. Examination of cells from his peripheral blood, skin biopsy, lymph node biopsy, and metatarsal bone biopsy revealed malignant convoluted T cells. A T-lymphoblast cell line, HUT 102, was established from tumor cells derived from the lymph node biopsy. He was treated with concurrent whole-body electron-beam radiation therapy and combination chemotherapy (17), and had an apparent complete remission.



n cultures of peripheral blood lymphocytes from four of
-ATLA-positive monkeys.

1980

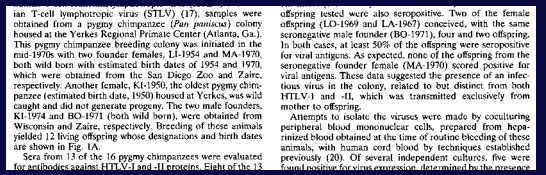
HTLV-2/STLV-2



12. W. E. VanHeyningen, *Nature (London)* **249**, 415 (1974).
13. ———, *J. Gen. Microbiol.* **31**, 375 (1963); F. Besancon, H. Ankel, S. Basu, *Nature (London)* **259**, 576 (1976); A. M. Haywood, *J. Mol. Biol.*

eases for statistical analysis and computer p
ting, V. Ginsburg and H. B. Pollard for crit
reading of the manuscript, and J. Mok for p
paring the manuscript.

11 August 1982



ian T-cell lymphotropic virus (STLV) (17), samples were obtained from a pygmy chimpanzee (*Pan paniscus*) colony housed at the Yerkes Regional Primate Center (Atlanta, Ga.). This pygmy chimpanzee breeding colony was initiated in the mid-1970s with two founder females, LI-1954 and MA-1970, both wild born with estimated birth dates of 1954 and 1970, which were obtained from the San Diego Zoo and Zaire, respectively. Another female, KI-1950, the oldest pygmy chimpanzee (estimated birth date, 1950) housed at Yerkes, was wild caught and did not generate progeny. The two male founders, KI-1974 and BO-1971 (both wild born), were obtained from Wisconsin and Zaire, respectively. Breeding of these animals yielded 12 living offspring whose designations and birth dates are shown in Fig. 1A.

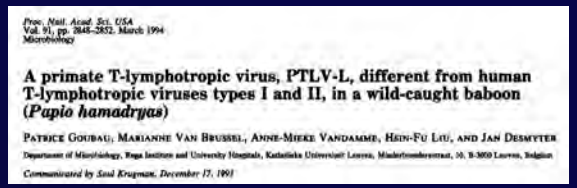
Sera from 13 of the 16 pygmy chimpanzees were evaluated

offspring tested were also seropositive. Two of the female offspring (LO-1969 and LA-1967) conceived, with the same seronegative male founder (BO-1971), four and two offspring. In both cases, at least 50% of the offspring were seropositive for viral antigens. As expected, none of the offspring from the seronegative founder female (MA-1970) scored positive for viral antigens. These data suggested the presence of an infectious virus in the colony, related to but distinct from both HTLV-I and -II, which was transmitted exclusively from mother to offspring.

Attempts to isolate the viruses were made by coculturing peripheral blood mononuclear cells, prepared from heparinized blood obtained at the time of routine bleeding of these animals, with human cord blood by techniques established previously (20). Of several independent cultures, five were

1982

HTLV-3/STLV-3



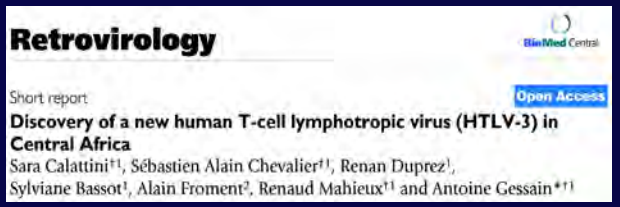
Proc. Natl. Acad. Sci. USA
Vol. 91, pp. 2848–2852, March 1994
Microbiology

A primate T-lymphotropic virus, PTLV-L, different from human T-lymphotropic viruses types I and II, in a wild-caught baboon (*Papio hamadryas*)

PATRICE GOUBAU, MARIANNE VAN BRUSSEL, ANNE-MIEKE VANDAMME, HSIN-FU LIU, AND JAN DESMYTER

Department of Microbiology, Rega Institute and University Hospitals, Katholieke Universiteit Leuven, Minderbroedersstraat, 10, B-3000 Leuven, Belgium

Communicated by Saul Krugman, December 17, 1993



Retrovirology

BioMed Central

Short report

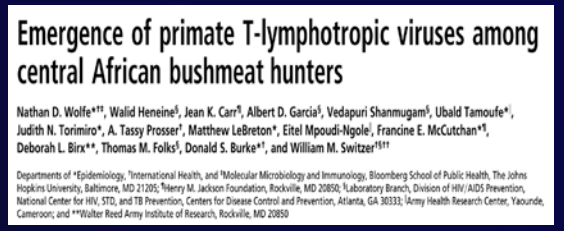
Open Access

Discovery of a new human T-cell lymphotropic virus (HTLV-3) in Central Africa

Sara Calattini[†1], Sébastien Alain Chevalier[†1], Renan Duprez[1], Sylviane Bassot[1], Alain Froment[2], Renaud Mahieux[†1] and Antoine Gessain[*†1]

1994

HTLV-4/STLV-4



Emergence of primate T-lymphotropic viruses among central African bushmeat hunters

Nathan D. Wolfe*[†‡], Walid Heneine[§], Jean K. Carr[§], Albert D. Garcia[§], Vedapuri Shanmugam[§], Ubald Tamoufe[¶], Judith N. Torimiro[¶], A. Tassy Prosser[‖], Matthew LeBreton*, Eitel Mpoudi-Ngole[¶], Francine E. McCutchan*[§], Deborah L. Birx**, Thomas M. Folks[§], Donald S. Burke*[†], and William M. Switzer[§§†]

Departments of *Epidemiology, [‖]International Health, and [§]Molecular Microbiology and Immunology, Bloomberg School of Public Health, The Johns Hopkins University, Baltimore, MD 21205; [§]Henry M. Jackson Foundation, Rockville, MD 20850; [§]Laboratory Branch, Division of HIV/AIDS Prevention, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA 30333; [¶]Army Health Research Center, Yaounde, Cameroon; and **Walter Reed Army Institute of Research, Rockville, MD 20850

0.1038/emi.2014.7

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www.nature.com/emi

ORIGINAL ARTICLE

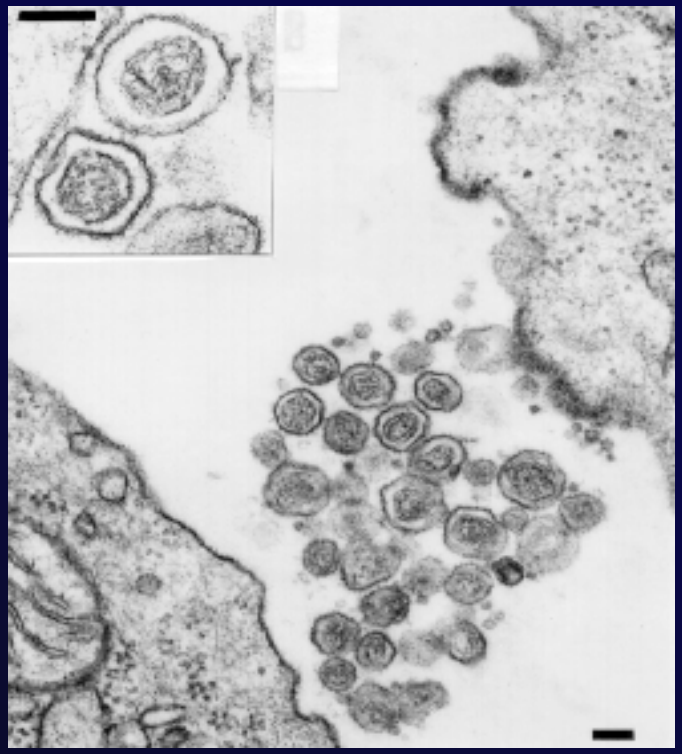
A gorilla reservoir for human T-lymphotropic virus type 4

Matthew LeBreton[1,2,3,*], William M Switzer[4,*], Cyrille F Djoko[2], Amethyst Gillis[2,3], Hongwei Jia[4], Michele M Sturgeon[4], Anupama Shankar[4], Haoqiang Zheng[4], Gerard Nkeunen[2], Ubald Tamoufe[2,3], Ahmadou Nana[2], Joseph Le Doux Diffo[2], Babila Tafon[5], John Kiyang[6], Bradley S Schneider[3], Donald S Burke[7] and Nathan D Wolfe[3,8,9]

2005

Human T Lymphotropic Viruses (1- 4)

Prototype: The Human Onco-Retrovirus HTLV-I



Extracellular Type C Retroviral particles
produced by a T lymphoid cell line established from the culture of the PBMCs of a patient with a TSP/HAM.
Gessain et al., 1989.

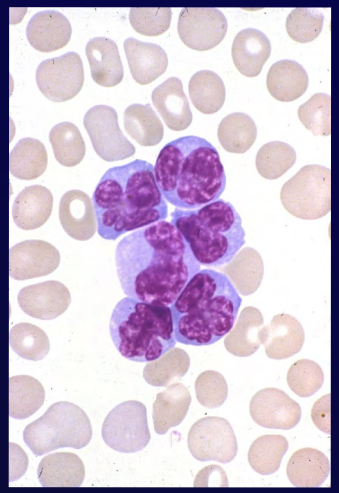
- **Discovery: 1980 NIH USA, 1981 Japan.**
- **Several associated diseases (hematological ATL, neurological TSP/HAM, dermatological ID, muscular Myositis,…)**
- **Peculiar epidemiology (foci, high endemic areas, > 5/10 millions of infected persons, increase with age and > in women).**
- **I*n vivo tropism*: CD4+ and CD8 + lymphocytes**
- **Clonal way of life = Great genetic stability ++**

Isolation of HTLV-1 1980, USA

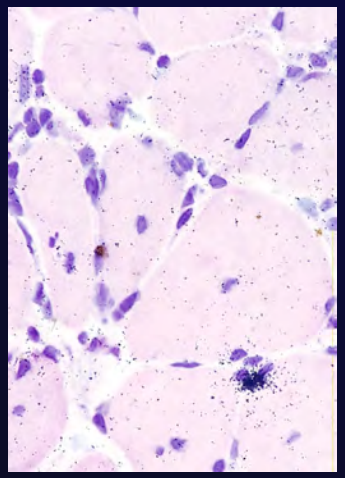
Description of ATL 1973-1977, Japan

Diseases associated with HTLV-1infection

ATL cells



Biopsy of a sIBM



DISEASES ASSOCIATED WITH HTLV-I INFECTION

Adult disease	Association
Adult T-cell leukaemia/lymphoma	++++
Tropical spastic paraparesis/HTLV-I-associated myelopathy	++++
Intermediate uveitis	+++
Infective dermatitis	+++
Myositis (polymyositis and sIBM)	+++
HTLV-I-associated arthritis	++
Pulmonary infiltrative pneumonitis	++
Invasive cervical cancer	+
Small cell carcinoma of lung	+
Sjögren disease	+

Childhood	Association
Infective dermatitis	++++
Tropical spastic paraparesis/HTLV-I-associated myelopathy (very rare)	++++
Adult T-cell leukaemia/lymphoma (very rare)	++++
Persistent lymphadenopathy	++

The strenght of association is based on epidemiological studies as well molecular data, animal models and intervention trials.
++++, proven association ; +++, probable association ; ++, likely association ; +, possible association.

SIBM : sporadic inclusion body myositis.

TSP/HAM patients

Gessain et al., lancet1985

Infective dermatitis patients

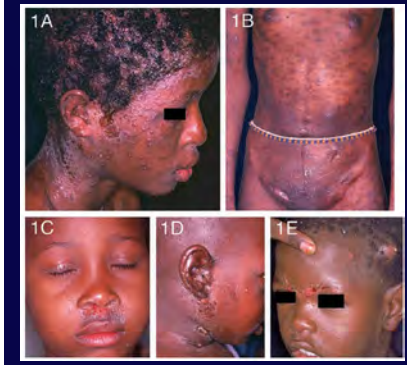


Fig. 1. Distribution of HAM and ATLL in Japan. Notice that distribution of myelopathy cases follows that of leukemia cases.

In Japan, 1 000 000 HTLV-1 carriers.

1000 cases of ATL each year.

1000 patients die of ATL each year.

The Life Time Risk of ATL among HTLV-1 Carriers

is around 6-7% for men and 2-3% for Women in Japan

The annual incidence of ATL among adut HTLV-1 carriers

is around 1.3-0.5 / 1000 (higher in men > women)

Discovery of the association between HTLV-1 infection and a chronic neuro-myelopathy frequent in tropical areas, especially the Caribbean region, named Tropical Spastic Paraparesis.

ANTIBODIES TO HUMAN T-LYMPHOTROPIC VIRUS TYPE-I IN PATIENTS WITH TROPICAL SPASTIC PARAPARESIS

A. GESSAIN
J. C. VERNANT
L. MAURS
F. BARIN
O. GOUT
A. CALENDER
G. DE THÉ

Laboratoire d'Epidémiologie et Immunovirologie des Tumeurs CNRS, Faculté de Médecine Alexis Carrel, Lyon, and Laboratoire de Virologie, Université F. Rabelais, Tours, France; and Service de Neurologie, Hospital La Meynard, Centre Hospitalier Régional de Fort de France, Martinique

Summary 10 out of 17 (59%) patients with tropical spastic paraparesis (TSP) had antibodies to human T-lymphotropic virus-I (HTLV-I), as did 5 out of 5 TSP patients with systemic symptoms. Only 13 out of 303 (4%) controls, made up of blood donors, medical personnel, and other neurological patients, had such antibodies. These findings suggest either that HTLV-I is neurotropic or that the virus or a related one contributes to the pathogenesis of TSP.

THE LANCET, AUGUST 24, 1985

Blood transfusion is a major risk factor for TSP/HAM development

Strong Epidemiological Data

THE LANCET, JULY 12, 1986

BLOOD TRANSFUSION AND HTLV-I ASSOCIATED MYELOPATHY

Third Department of Internal Medicine, Faculty of Medicine, Kagoshima University, Kagoshima 890, Japan — MITSUHIRO OSAME, SHUJI IZUMO, AKIHIRO IGATA

Institute of Cancer Research, Faculty of Medicine, Kagoshima University — MAKOTO MATSUMOTO, TADASHI MATSUMOTO

Department of Virology, Faculty of Medicine, Kagoshima University — SHUNRO SONODA

Kagoshima City Hospital — MITSUTOSHI TARA

Department of Epidemiology, National Institute for Minamata Disease — YOSHISADA SHIBATA

Group	Age (mean ± SD) (yr)	History of blood transfusion	Odds ratio
HAM	47 ± 15	9/23 (39%)	. .
ATLL*	57 ± 12	1/23	14·1 (p < 0·005)
Inpatients†	50 ± 16	1/33	20·6 (p < 0·001)
Hospital staff	30 ± 8	8/296 (2·7%)	231·1 (p < 0·001)

*History before onset of symptoms.
†3rd department of internal medicine, Kagoshima University (ATLL and HAM excluded).

A) In a case-control study in Japan, more patients with TSP/HAM reported a history of blood transfusion (20%) than did controls (healthy general population (3%), hospitalized neurological patients (5%)).

B) **In the first two years of screening blood donors for HTLV-1 in Japan, the number of reported cases of TSP/HAM has decreased of 16%.**

Several Case Reports with Molecular Evidence Linking Donor and Recipient

HTLV-I–associated myelopathy associated with blood transfusion in the United States:
Epidemiologic and molecular evidence linking donor and recipient

J.E. Kaplan, MD; B. Litchfield; C. Roumult, MD; M.D. Lairmore, PhD; C.-C. Luo, PhD; L. Williams, PhD; B.J. Brew, MD; R.W. Price, MD; R. Janssen, MD; R. Stoneburner, MD; C.-Y. Ou, PhD; T. Folks, PhD; and B. De, PhD

Article abstract—Six months after receiving 58 units of blood components, a 65-year-old white man from New York City, with no other risk factors for human T-lymphotropic virus type I (HTLV-I) infection, developed HTLV-I–associated myelopathy/tropical spastic paraparesis (HAM/TSP). Investigation of blood donors identified a 25-year-old white Hispanic woman from Florida whose platelets had been given to the patient and who was seropositive for the virus on a serum specimen obtained 2 years after the donation. She was born in Cuba and had had 2 sexual relationships with men who either had been born in or had resided in the Caribbean. Polymerase chain reaction (PCR) studies of peripheral blood mononuclear cells indicated that both donor and recipient were infected with HTLV-I. Molecular studies of a 595-nucleotide sequence in the 5′ envelope region of HTLV-I indicated that the viruses from donor and recipient were identical in each of 32 positions in which published HTLV-I sequences demonstrate molecular heterogeneity; the donor and recipient viruses were also identical in 2 additional positions in which they differed from all published sequences. Transfusion-associated HAM/TSP has occurred in the United States, but additional cases should be prevented by screening blood donations for HTLV-I. Molecular studies of HTLV-I may prove useful in defining the genetic heterogeneity of HTLV-I isolates in the United States and in studying transmission of this virus.

NEUROLOGY 1991;41:192-197

MEDICAL INTELLIGENCE

RAPID DEVELOPMENT OF MYELOPATHY AFTER HTLV-I INFECTION ACQUIRED BY TRANSFUSION DURING CARDIAC TRANSPLANTATION

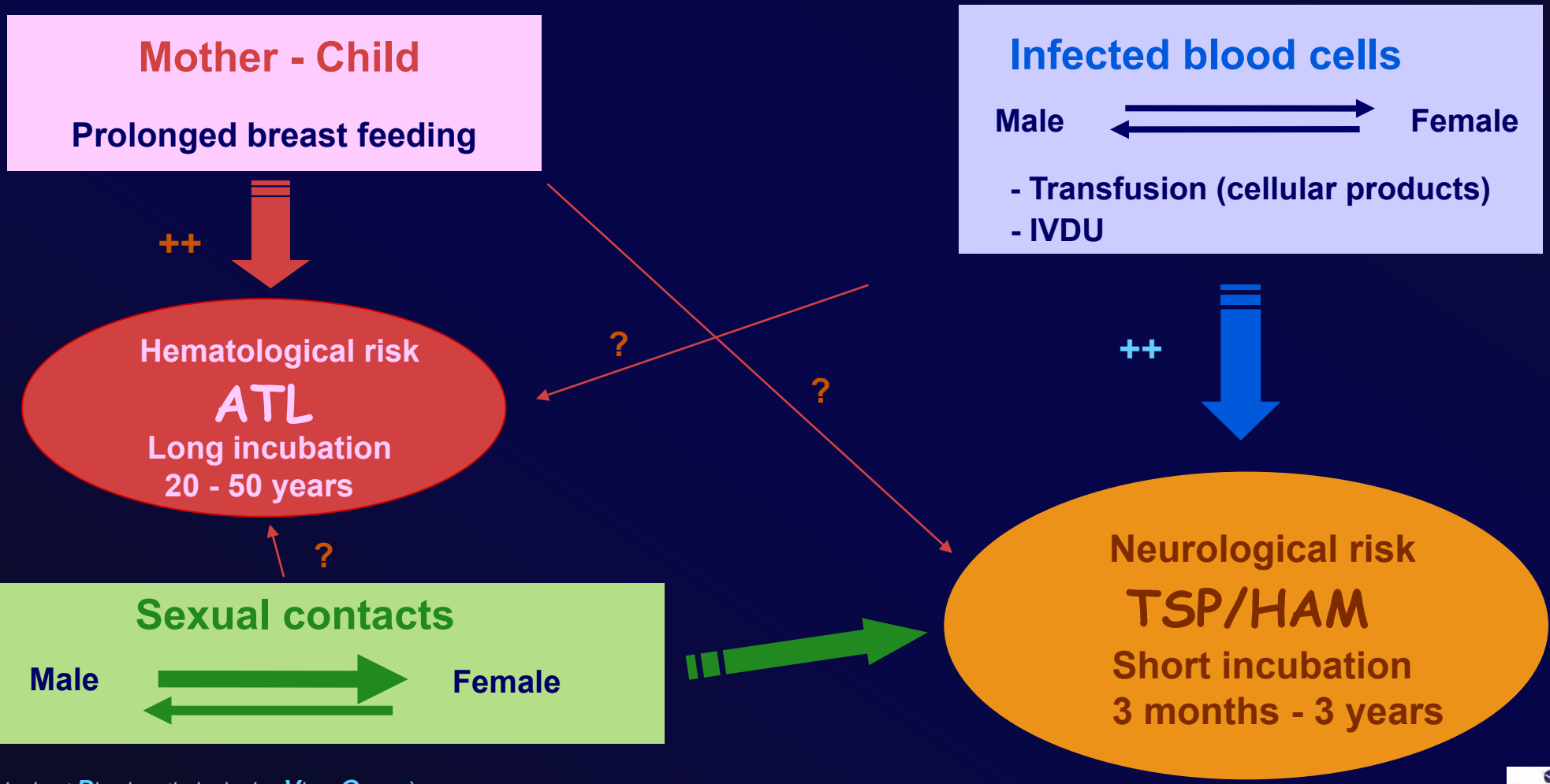
OLIVIER GOUT, M.D., MICHEL BAULAC, M.D., ANTOINE GESSAIN, M.D., FRANK SEMAH, M.D., FORTUNA SAAL, M.D., JORGE PÉRIÈS, M.D., PH.D., CHRISTIAN CABROL, M.D., CATHERINE FOUCAULT-FRETZ, M.D., DOMINIQUE LAPLANE, M.D., FRANÇOIS SIGAUX, M.D., AND GUY DE THÉ, M.D., PH.D.

INSTITUT PASTEUR

In most of the high endemic areas, HTLV-1 is mainly disseminated and maintained in the human population through **intra-familial transmission**

(mother-to-child and by sexual intercourses).

More rarely, transmission may also occur by transfusion or Intra-venous drug use.



What are the different modes of transmission of HTLV-1 and what is their relative importance in the populations of infected persons?

1) **Sexual transmission** mainly from male to women. Most probably responsible for the **great majority of infected persons in endemic regions** and for the **increase in seroprevalence with age among women**.

2) **Mother-to-child transmission** mainly linked to prolonged breastfeeding >6 months. Responsible for a small proportion of HTLV-1 infected persons.

3) **Transmission via contaminated blood products** (cell-associated virus) during transfusion, in IDUs, when using infected syringes or non-sterile ustensils. **Rare**, but present in endemic regions and disappearing in regions where blood donors are screened (Japan, USA, Brazil, Europe,..)

4) **Transmission during organ transplantation. Rare**

5) **Transmission in a religious/ritual context** as self flagellation/scarification. **Rare**

6) **Zoonotic transmission** mainly through severe bites by a **STLV-1** infected monkeys or apes among hunters in Central Africa. **Rare**

What is the current real geographical distribution of HTLV-1 and how many individuals are infected worldwide ?

This is difficult to estimate due to the following factors:

1) **Several large and highly populated regions/areas have not been investigated for HTLV-1** as India/China and North and East Africa.

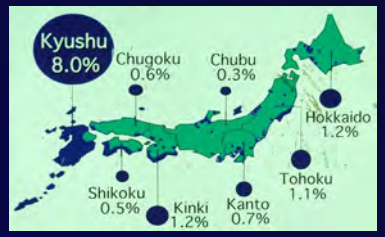
2) Results of HTLV-1 screening serology should be tested by a **specific confirmatory test as WB, Innolia and/or PCR.**

3) **Most of the studies concern blood donors and pregnant women.** Very few large population-based study.

4) HTLV-1 **distribution is not homogenous.** Mainly present as **small foci** or **clusters of high or very prevalence with nearby quite low endemic area.**

The origin of this puzzling geographical or often ethnic distribution, associated with high prevalence is not well explained, but is most likely linked to a founder effect in certain groups, with the persistence of a high viral transmission rate

The major modes of transmission **coud be different among the populations with the highest prevalences : Central African Pygmies, Indigenous Australians, Inhabitants of South Japan, Mashhad (Iran), Haut-Ogoué (Gabon) and villages in DRC,....**



Indigenous Australians have one of the highest HTLV-1prevalence in the world

Such high prevalences have been already reported in some very high endemic areas

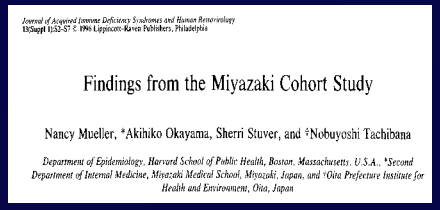

BMC Public Health

RESEARCH ARTICLE Open Access

Human T-Lymphotropic Virus type 1 infection in an Indigenous Australian population: epidemiological insights from a hospital-based cohort study


PLOS NEGLECTED TROPICAL DISEASES

Very high prevalence of infection with the human T cell leukaemia virus type 1c in remote Australian Aboriginal communities: Results of a large cross-sectional community survey


Findings from the Miyazaki Cohort Study

Nancy Mueller, *Akihiko Okayama, Sherri Stuver, and †Nobuyoshi Tachibana

Villagers from South Japan

Noir-Marron (population of African Origin) in French Guyana, South America

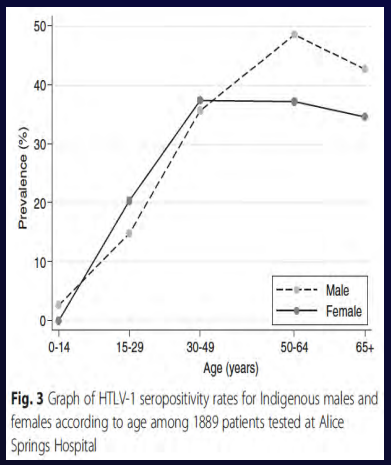
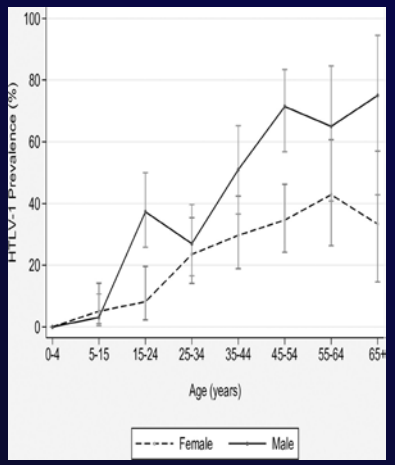
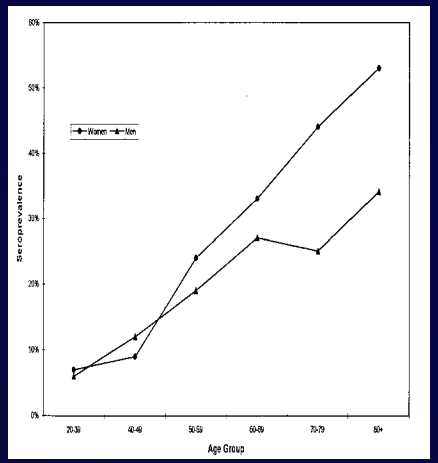
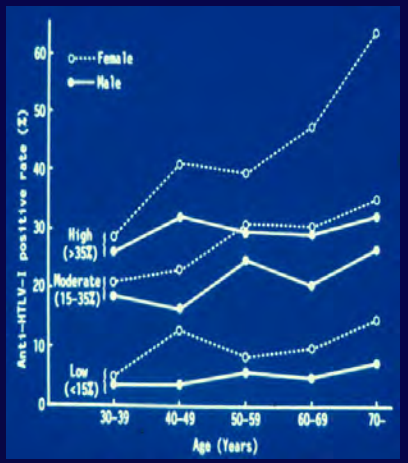
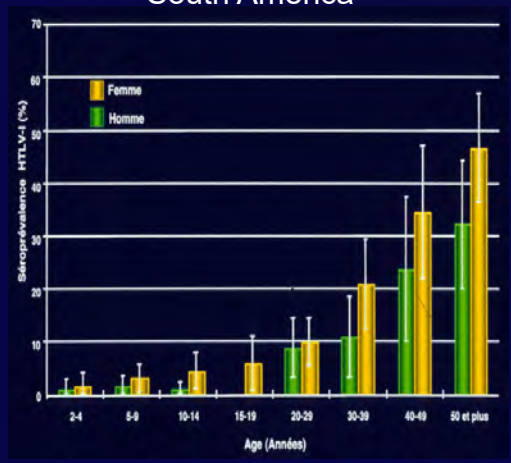


Fig. 3 Graph of HTLV-1 seropositivity rates for Indigenous males and females according to age among 1889 patients tested at Alice Springs Hospital









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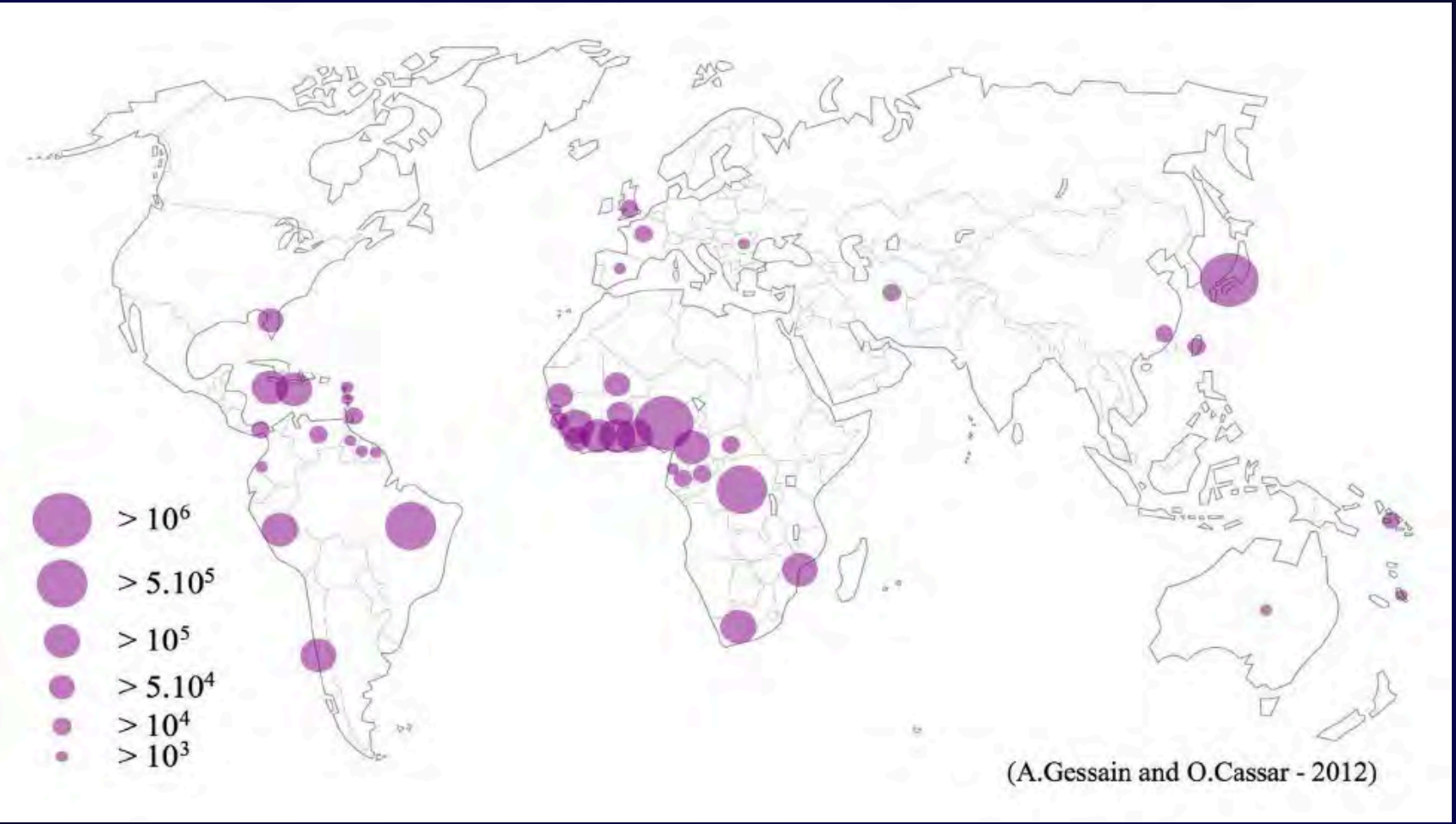
Minimum estimate of 5-10 million HTLV-1 infected carriers based on available data for 1.5 billion people from known endemic areas

The actual number is probably much higher

World distribution major HTLV-1 endemic foci

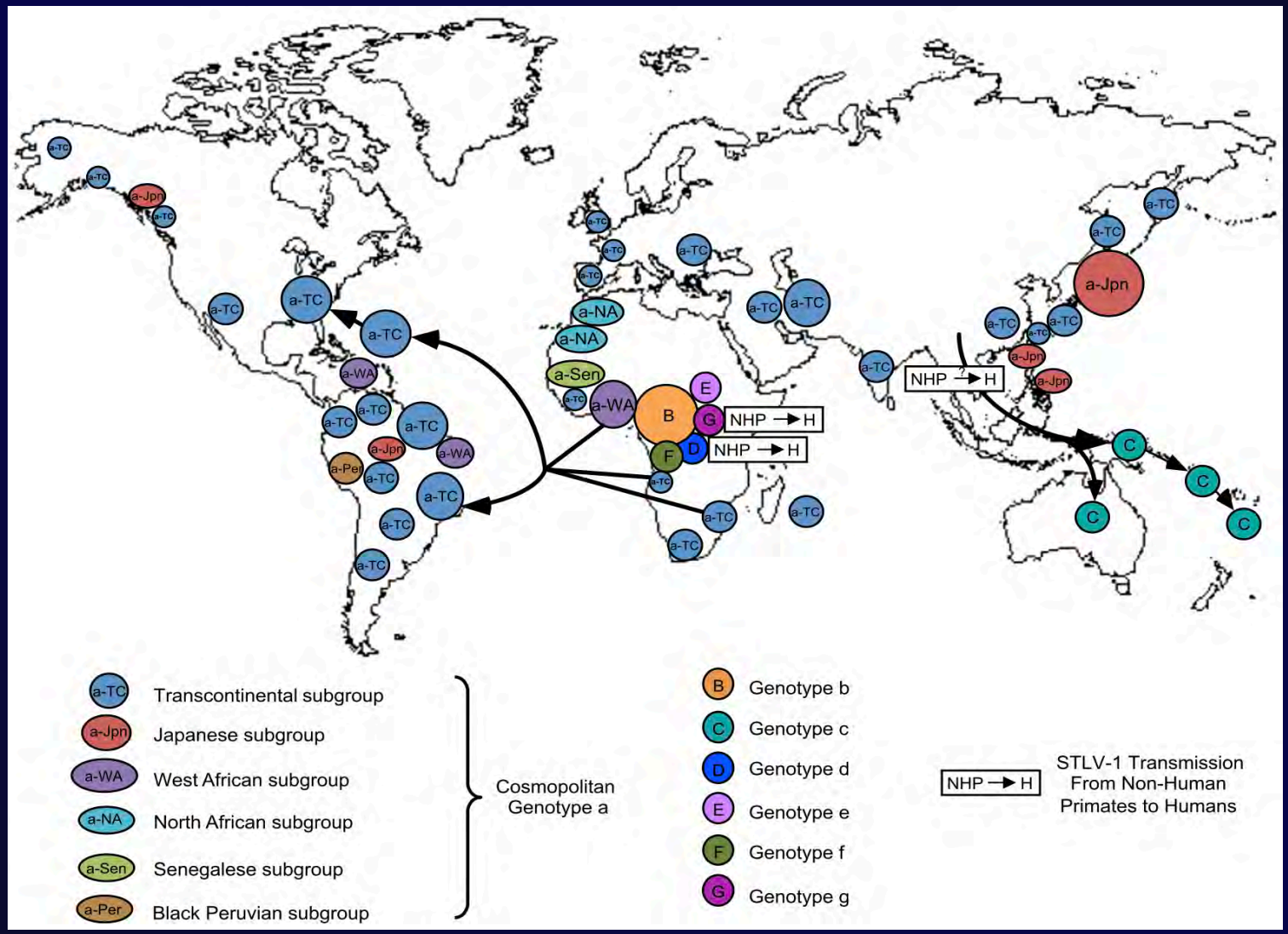
Prevalence can reach >>20/30% in adults > 50 years



Gessain and Cassar: Frontiers in Microbiology, 2012

Map of geographical distribution of HTLV-1 (a–g) genotypes and main modes of viral dissemination through movements of infected populations

Low genetic variability with 7 different HTLV-1 main genotypes (a-g) with specific geographical distribution.



Afonso, Cassar, Gessain. Retrovirology, 2019

HTLVs originate from STLVs found in Apes and Monkeys through interspecies transmission especially by severe bites in central Africa

PTLV = Primate T-lymphotropic viruses

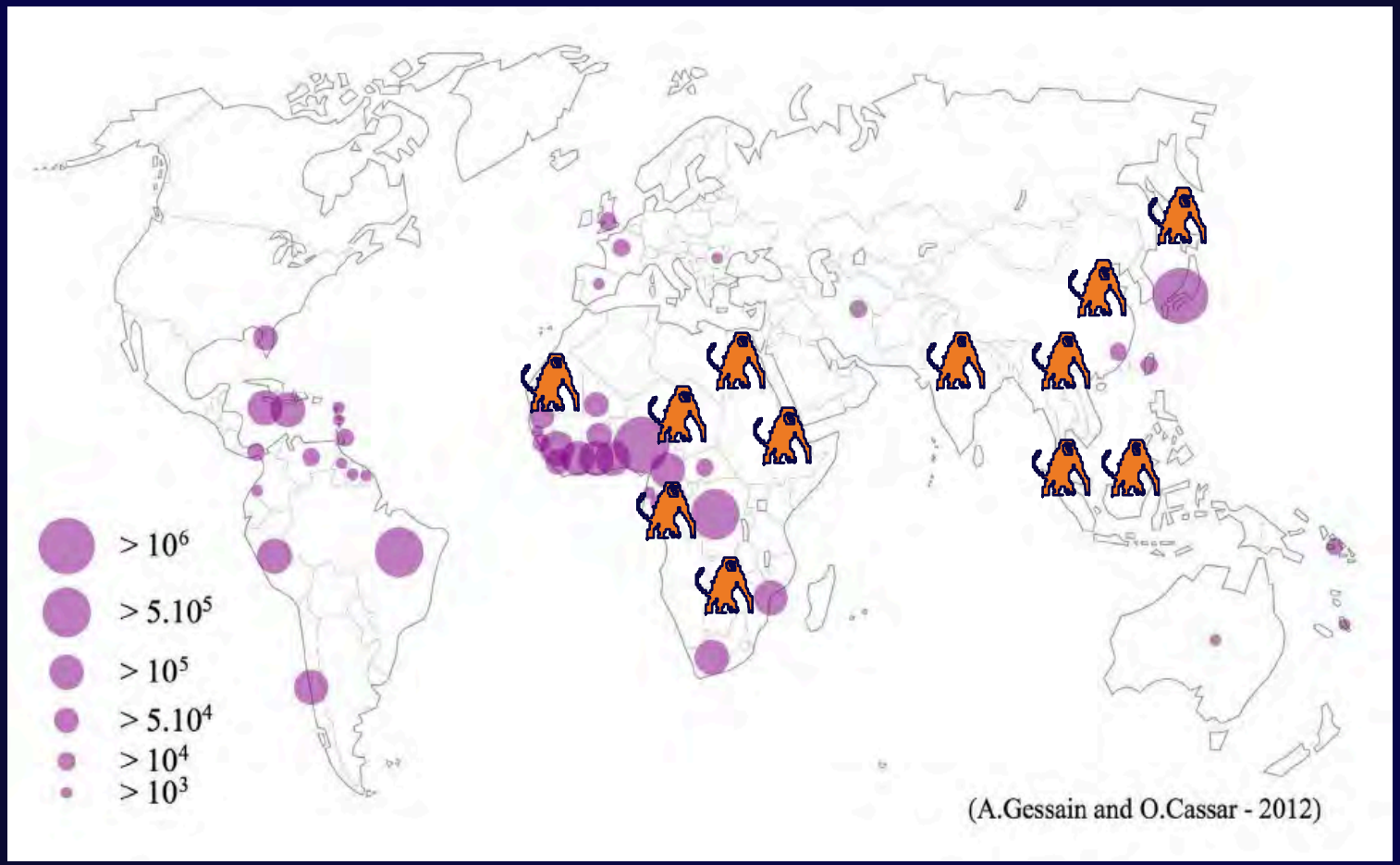
→ If found in NHP = STLV

→ If found in Human = HTLV

1) Some of the infected monkeys develop a typical ATL with clonal integration of STLV-1 provirus in the tumor cells.

2) STLV-1 infection is widespread in Old World monkey and ape species (chimpanzee, gorilla, mandrill, AGM, macaques, Orang-utan,….).

3) The simian origin for most HTLV-1 genotypes is known except for the most frequent one HTLV1a cosmopolitan genotype.



In 2012, the EU Commission requested ECDC to construct a map indicating all the HTLV-1 high prevalence areas in the world.

EPVO unit, thanks to its expertise, was asked to respond to a request for offer entitled : " *Systematic Review of Scientific Evidence on the Prevalence of HTLV-1 Infection*"

By analysing more than 1000 papers and hundreds of abstracts, we provided the first complete epidemiological data (maps and tables) for the 203 world's countries.

Figure 3. HTLV-1 prevalence in sovereign states and territories of Europe[3]

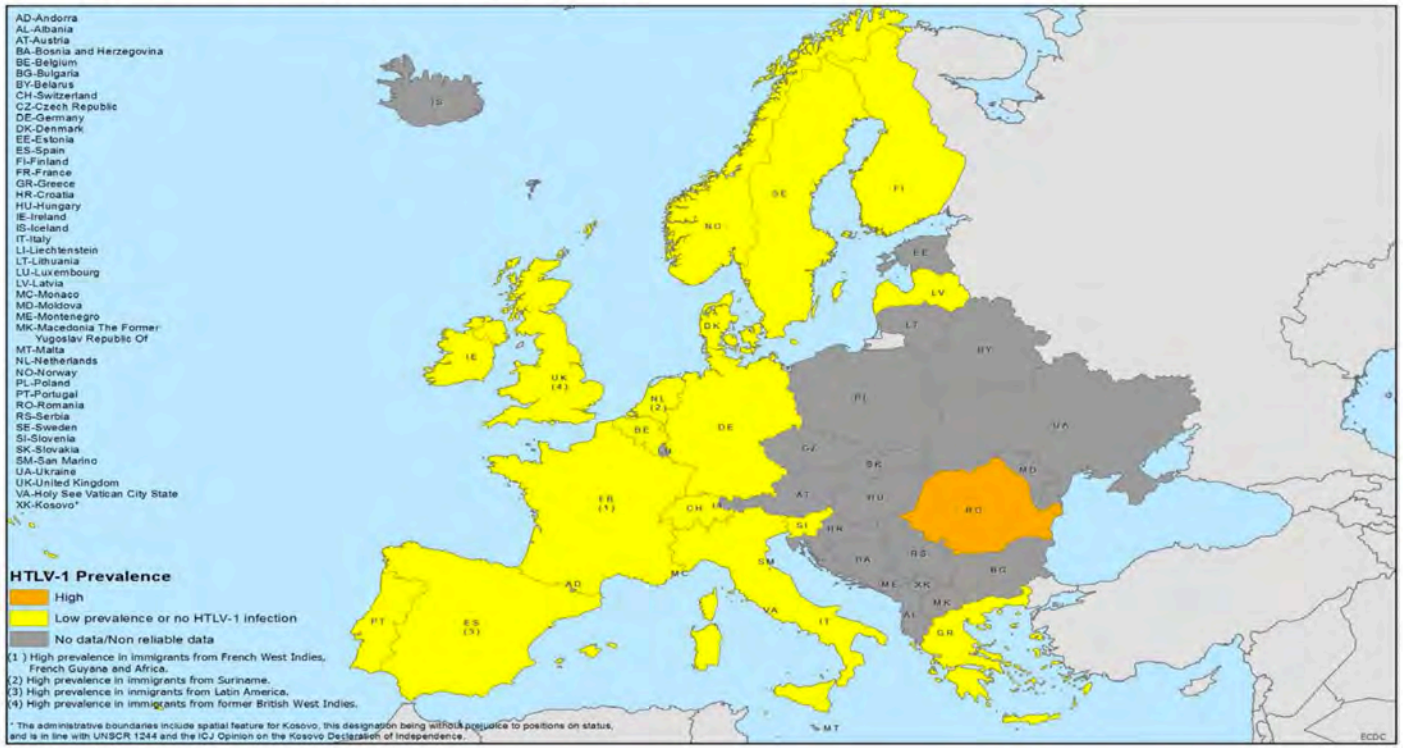


Figure 2. HTLV-1 prevalence in sovereign states and territories of Central/South America and the Caribbean Islands[2]

Europe (UK, France, Spain,..) Individuals originating from high HTLV-1 endemic areas (Caribbean area, South America and Africa,..), except Romania.

Continent / Country	Population°	HTLV-1 range	
EUROPE			
United kingdom**	63 047 162	20 000	30 000
France	65 630 692	15 000	25 000
Spain	47 042 984	1 000	8 000
Romania	21 848 504	3 000	15 000

✓ In Europe, HTLV-1 is rare, except in people who have immigrated from countries where HTLV-1 is highly endemic, such as The UK, France and Spain, mainly from The West Indies, sub-Saharan Africa and South America. The only "true" endemic region for HTLV-1 in Europe is Romania even if the exact risk factors associated with this high seroprevalence are unknown

HTLV-1 Technical report, ECDC, 2012

✓ Indeed, the Seroprevalence in FTBD is around **10 times higher** than in **France** and **The UK** *(Laperche S. et al., Vox sang, 2009)* and around **20 times Higher than in Spain** *(Piron M. et al., Viruses, 2022)*

Country	Number of tested ind.	Collection date	Nb HTLV-1+	Rate per 10,000	HTLV-1 + (%)	Source, y
Romania	215,732 (FTBD)	2003-2005	115	5.33	0.053	Laperche S. *et al*., Vox Sang, 2009
France	1,115,030 (FTBD)	2003-2005	54	0.48	0.0048	Laperche S. *et al*., Vox Sang, 2009
UK	850,801 (FTBD)	2003-2005	40	0.47	0.0047	Laperche S. *et al*., Vox Sang, 2009
Spain	2,114,891 (All BD)	2008-2017	46	0.22	0.0022	Piron M., *et al*., Viruses, 2022

HTLV-1 Epidemiological and Clinical studies in Romania

Indeed, "ancient" seroepidemiological studies have reported the presence of HTLV-1 in Romanian individuals

1994

Eur J Haematol 1994: 52: 117–118
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EUROPEAN JOURNAL OF HAEMATOLOGY
ISSN 0902-4441

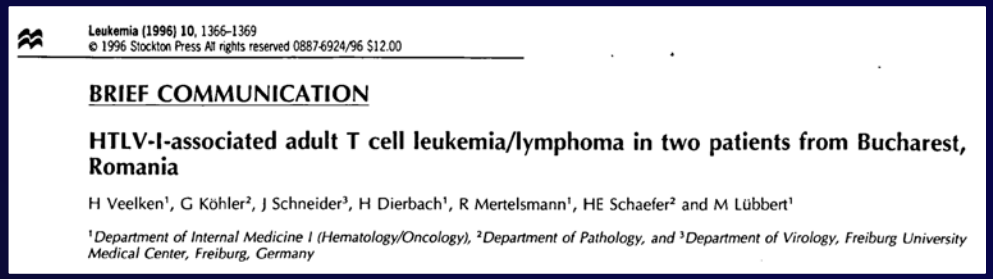
Letters to the Editor

HTLV-I in Romania

Correspondence:
Ludovic Paun*, Doinita Ispas*, Annarosa Del Mistro** and Luigi Chieco-Bianchi**
*Clinic "Dr. Victor Babes" for Infectious and Tropical Diseases, University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania; **Institute of Oncology, University of Padova, Italy.
Postal address: Annarosa Del Mistro, Institute of Oncology, via Gattamelata, 64 – 35128 Padova, Italy.

Several sporadic case report and ATL case-series have also been described

1996



Leukemia (1996) 10, 1366–1369

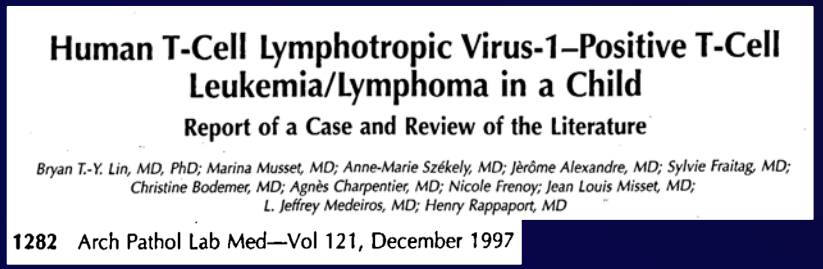
BRIEF COMMUNICATION

HTLV-I-associated adult T cell leukemia/lymphoma in two patients from Bucharest, Romania

H Veelken[1], G Köhler[2], J Schneider[3], H Dierbach[1], R Mertelsmann[1], HE Schaefer[2] and M Lübbert[1]

[1]Department of Internal Medicine I (Hematology/Oncology), [2]Department of Pathology, and [3]Department of Virology, Freiburg University Medical Center, Freiburg, Germany

1997

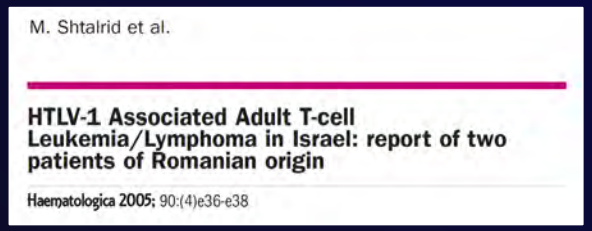


Human T-Cell Lymphotropic Virus-1–Positive T-Cell Leukemia/Lymphoma in a Child

Report of a Case and Review of the Literature

Bryan T.-Y. Lin, MD, PhD; Marina Musset, MD; Anne-Marie Székely, MD; Jèrôme Alexandre, MD; Sylvie Fraitag, MD; Christine Bodemer, MD; Agnès Charpentier, MD; Nicole Frenoy; Jean Louis Misset, MD; L. Jeffrey Medeiros, MD; Henry Rappaport, MD

2005



M. Shtalrid et al.

HTLV-1 Associated Adult T-cell Leukemia/Lymphoma in Israel: report of two patients of Romanian origin

Haematologica 2005; 90:(4)e36-e38

2019

blood

Results from Treatment of a Large Cohort of ATL Patients from a Country with High HTLV1 Prevalence

Horia Bumbea, MD PhD,[1,2] Ambroise Marçais, MD PhD,[3,4] Daniel Coriu, MD PhD,[4,5] Alina Daniela Tanase, MD PhD,[4,6] Andrei Colita, MD PhD,[4,7] Alexandru Bardas, MD,[4] Anca Roxana Lupu, MD PhD,[4,8] Ana-Maria Vladareanu, MD PhD,[9,10,11] Minodora Cezarina Onisai, MD PhD,[4,10,11] Viola Maria Popov, MD PhD MSc,[12] Iuliana Iordan, MD,[4,10] Magda Diana Cisleanu, MD PhD,[4,10,11] Daniela Stefania Vasile, MD PhD,[4,11] Cristina Maria Ciufu, MD PhD,[4,11,13] Zsofia Varady, MD PhD,[4,14] Oana Gabriela Craciun, MD,[4,15] Daniela Georgeta Georgescu, MD PhD,[4,16] Mihaela Andreescu, MD PhD,[4,16] Cristina Mambet, MD,[4,17] Carmen C. Diaconu, PhD,[4,17] Laura Necula, PhD,[4,17] Monica Bunaciu,[4,18] Adriana Necula,[4,19] Stefan N Constantinescu, MD PhD[17,20] Olivier Hermine, MD PhD[4,21]

2020

Journal of Clinical Medicine

MDPI

Article

Allogeneic Stem Cell Transplantation for Adult T-Cell Leukemia/Lymphoma—Romanian Experience

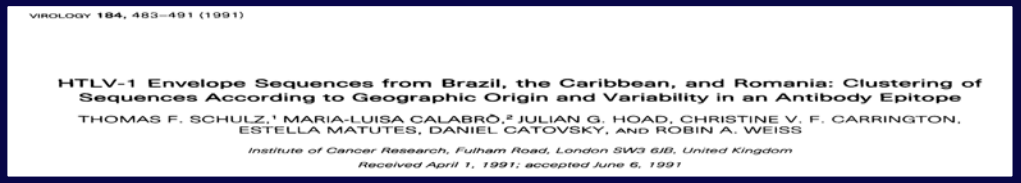
Alina D. Tanase [1,2], Andrei Colita [3,4,*], Oana G. Craciun [1], Lavinia Lipan [1], Zsofia Varady [1], Laura Stefan [1], Adela Ranete [1], Sergiu Pasca [5], Horia Bumbea [4,6], Mihaela Andreescu [7], Viola Popov [7], Alexandru Bardas [8], Daniel Coriu [4,8], Anca Roxana Lupu [3,4], Ciprian Tomuleasa [9,10], Anca Colita [1,11] and Olivier Hermine [12,13]

J. Clin. Med. 2020, 9, 2417; doi:10.3390/jcm9082417

HTLV-1 Genetic studies in Romania

Characterization of partial genomic sequences derived from Romanian HTLV-1 isolates

1991



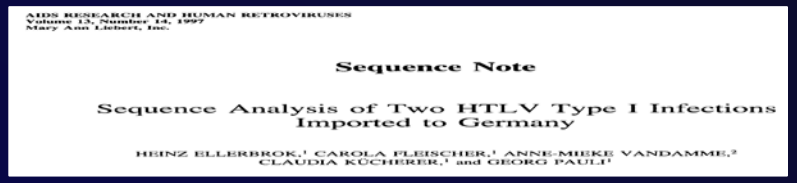
VIROLOGY 184, 483–491 (1991)

HTLV-1 Envelope Sequences from Brazil, the Caribbean, and Romania: Clustering of Sequences According to Geographic Origin and Variability in an Antibody Epitope

THOMAS F. SCHULZ,[1] MARIA-LUISA CALABRÒ,[2] JULIAN G. HOAD, CHRISTINE V. F. CARRINGTON, ESTELLA MATUTES, DANIEL CATOVSKY, AND ROBIN A. WEISS

Institute of Cancer Research, Fulham Road, London SW3 6JB, United Kingdom

Received April 1, 1991; accepted June 6, 1991



AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 13, Number 14, 1997
Mary Ann Liebert, Inc.

Sequence Note

Sequence Analysis of Two HTLV Type I Infections Imported to Germany

HEINZ ELLERBROK,[1] CAROLA FLEISCHER,[1] ANNE-MIEKE VANDAMME,[2] CLAUDIA KÜCHERER,[1] and GEORG PAULI[1]

1997

Limited number of sequences and genetic information

Molecular studies						
Date	**Patient**	**Birth place**	**Age, y**	**Gender**	**HTLV-1 Genomic region**	**Source, y**
1991	H990	Romania	34	M	Env (complete)	Schulz T, Virology, 1991
1997	RKI2-Rom	Romania	42	NA	Env (complete), LTR	Ellerbrok H, AIDS Res Hum Retrovir, 1997

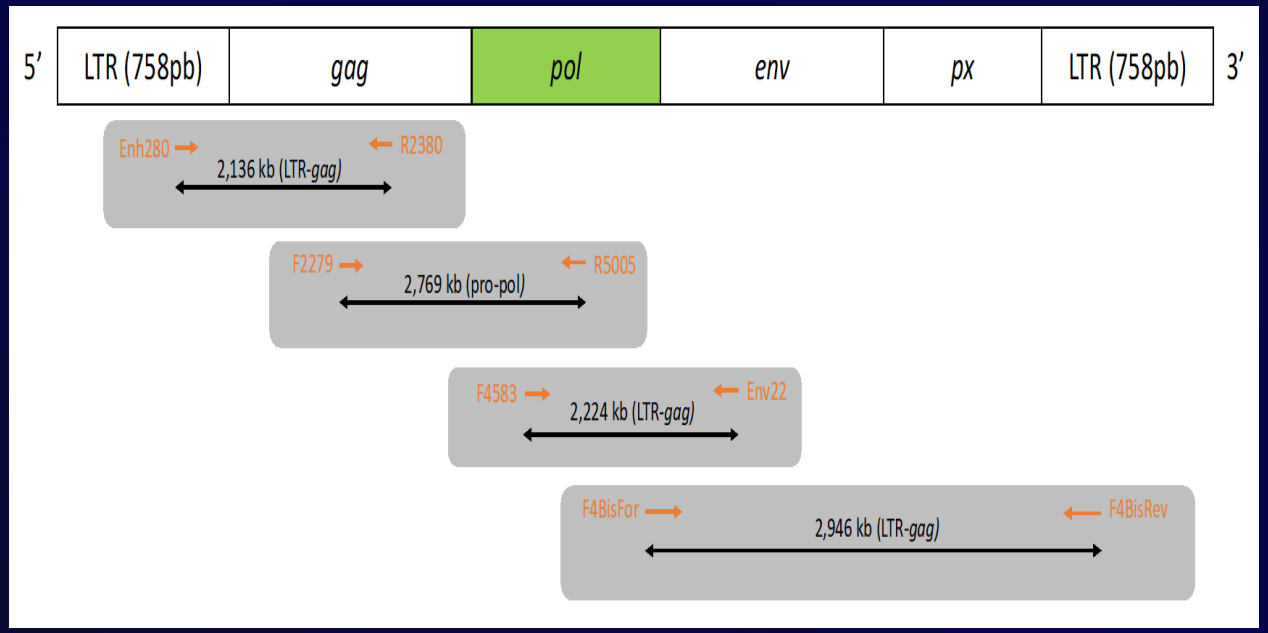
Study of 8 Romanian patients with ATL : Clinico-epidemiological data

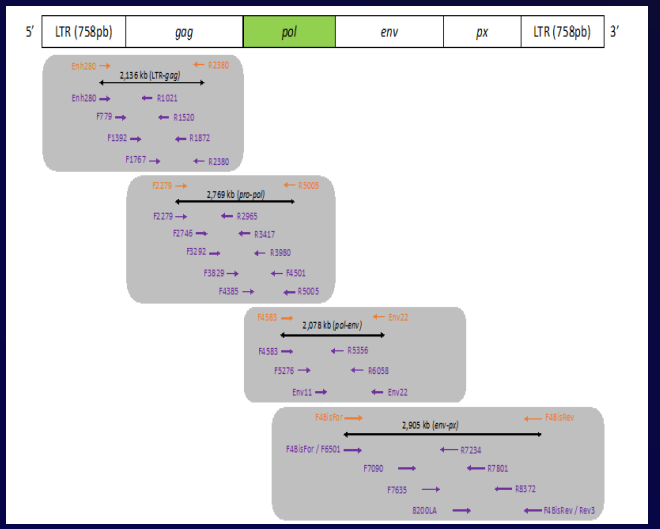
ID	Country	Age (y)	Gender	ATL clinical status	HTLV-1 status of Relatives	HTLV-1 aquisition risk factors	PVL (%)*
NIC.D	Romania	29	F	Chronic	Seronegative mother	Neonatal transfusion	40
RAD.C	Romania	52	F	Acute	Seronegative mother	Not breastfeeding	>50
RAD.P	Romania	39	F	Acute	Seronegative mother	Not breastfeeding	>50
BUD.N	Romania	26	M	Acute	Unknown	Unknown	31
GRO.A	Romania	42	F	Chronic	Unknown	Unknown	51
USU.S	Romania	48	M	Chronic	Unknown	Unknown	40
PH523	Romania	77	F	Lymphoma	Unknown	No transfusion event	NA
PH630	Romania	NA	F	NA	Unknown	Unknown	NA

✓Collaborative study mainly with the hematology department of the Necker Hospital in Paris (O. Hermine, A. Marçais and E-M. Deruelle) and hematological colleagues in Romania

HTLV-1 Genetic study: Material and Methods

DNA extraction from PBBCs and PCR amplification of 4 genomic fragments (F1-F4) with 4 different primers sets

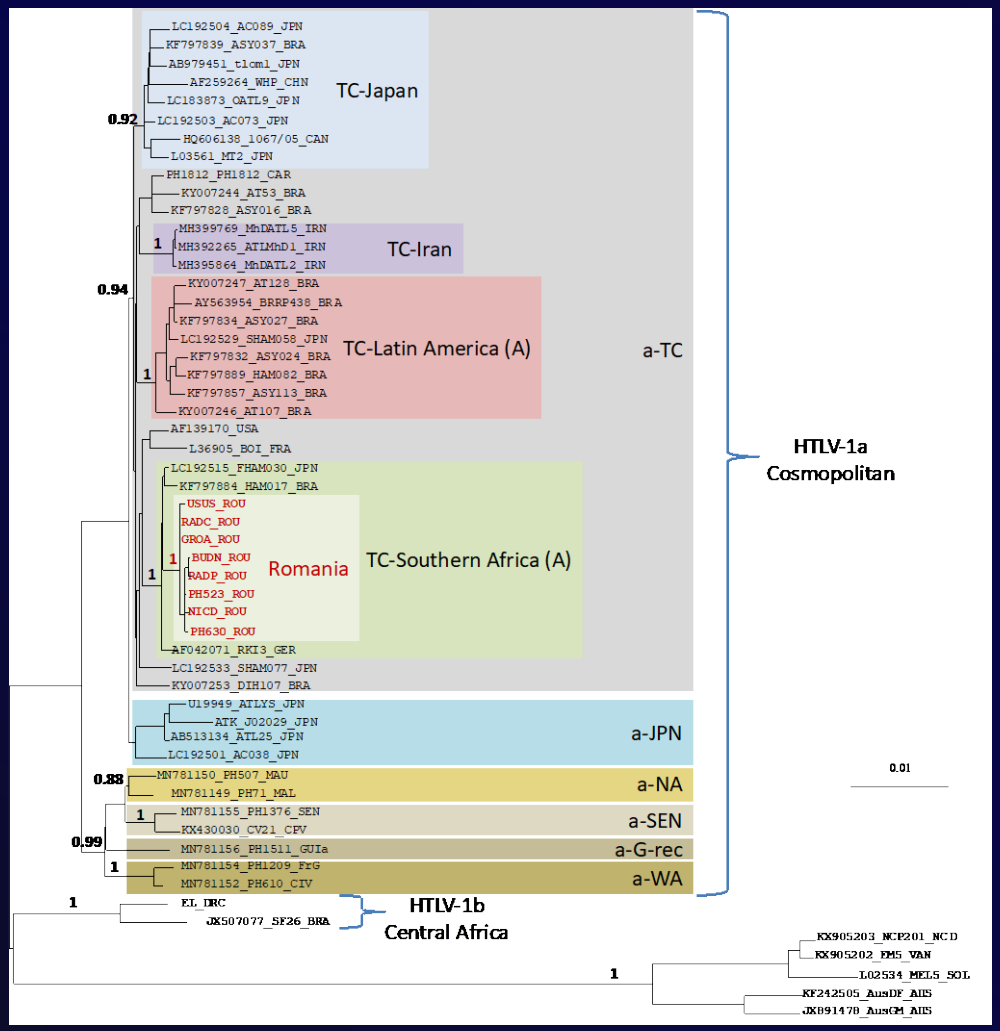




High fidelity Hot start Phire DNA polymerase

The complete proviral sequence was obtained by direct sequencing using 16 pairs of overlapping primers

HTLV-1 Genetic study: Phylogenetic analyses (full genome)

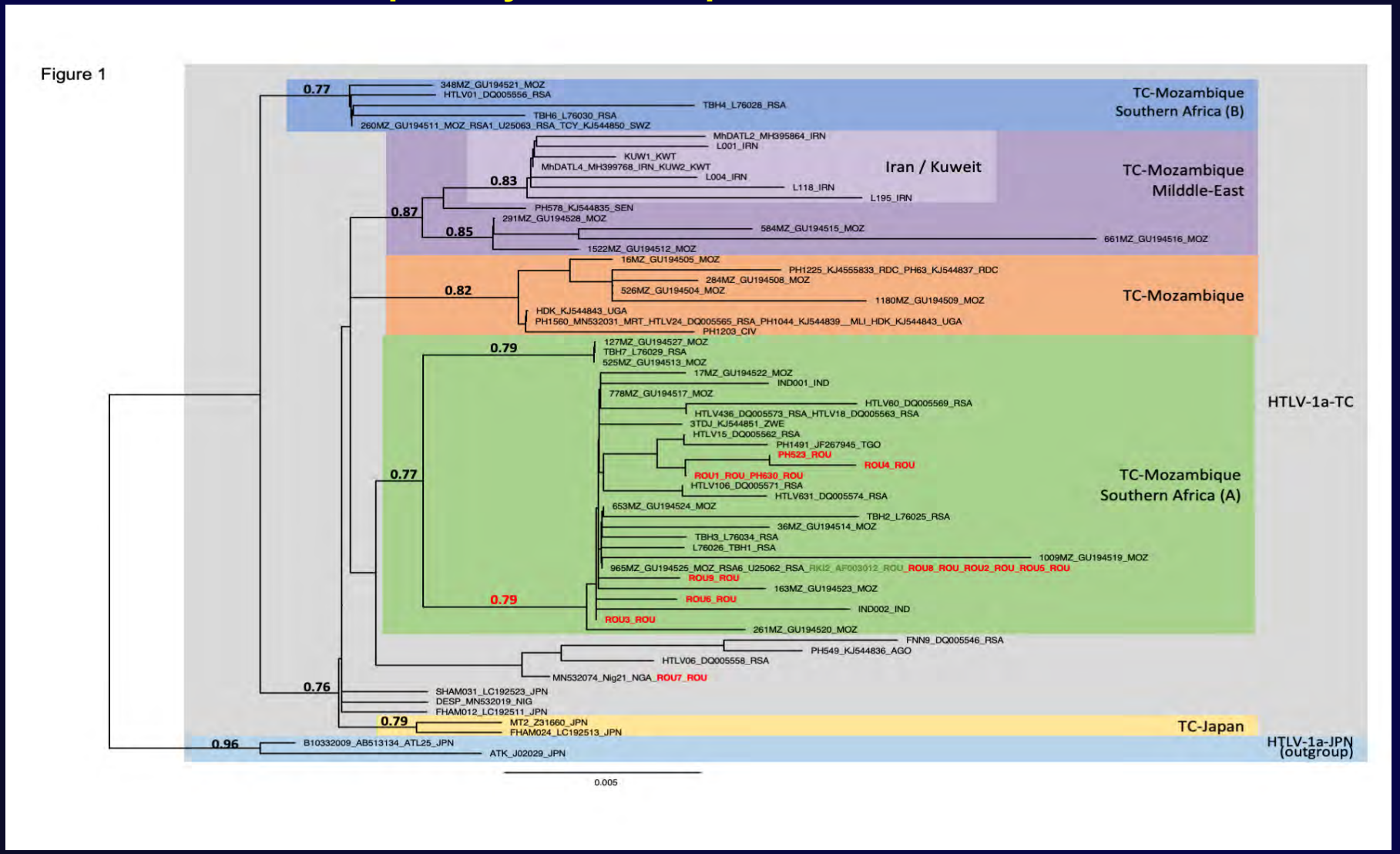


ML
8,160-bp
Bootstrap, 1000

- Comparison of an **8,160-bp fragment** of the complete HTLV-1 genome, obtained from the **8 Romanian individuals** and **47 reference strains**, shows that the **proviral Romanian strains are very close to each other** with nucleotide identity ranges from **99.8% to 100%** (0-18 different bases)
- Phylogenetic analysis clearly indicates that **the 8 new Romanian HTLV-1 strains** belong to the **Cosmopolitan HTLV-1-a genotype** and the **Transcontinental subgroup (a-TC)**
- If we considered the clades defined and named according to LTR analyses *(Vicente AC. et al., PLOS NTD, 2011 and Afonso PV. et al., Retrovirology, 2029)*, these strains are included in a **specific « Romania » clade,** strongly phylogenetically supported, and **within the TC-Southern Africa subgroup**

•LTR sequences analysis, including 70 reference strains (without South American ones), confirm that the new HTLV-1 Romanian strains belong to the HTLV-1-a TC subgroup and are different from strains found Japan and Middle-East. They are close to the only strain already characterized in a Romanian individual (RKI2) and close to strains from Southern Africa and especially Mozambique and South Africa

Figure 1



Deciphering the origin of HTLV-1 in Romania requires a

multidisciplinary approach

involving in depth epidemiological study, associated with genetic and historical research.

Difficult because retrospective study, on facts that are already old, asssociated with public health decisions taken at least more than 40 years ago (ATL).

It is esential to pursue surveillance and research efforts to limit the spread of this oncogenic retrovirus in Romania.

HTLV-1 in Spain

Contents lists available at ScienceDirect
International Journal of Infectious Diseases
journal homepage: www.elsevier.com/locate/ijid

Late presentation of human T-lymphotropic virus type 1 infection in Spain reflects suboptimal testing strategies

Carmen de Mendoza[1,**], Leire Pérez[2], Mario Fernández-Ruiz[3], María José Pena[4], José Manuel Ramos[5], Alberto Richart[6], María Piron[7], Ariadna Rando[8], Elisenda Miró[9], Gabriel Reina[10], Beatriz Encinas[1], Silvia Rojo[11], Antonio Manuel Rodriguez-Iglesias[12], Rafael Benito[13], Antonio Aguilera[14], Ana Treviño[15], Octavio Corral[15], Vicente Soriano[15,*]

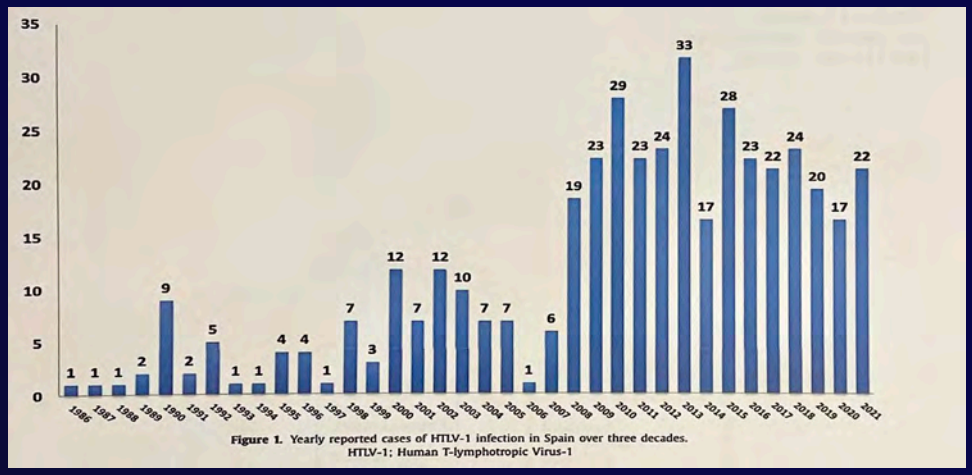
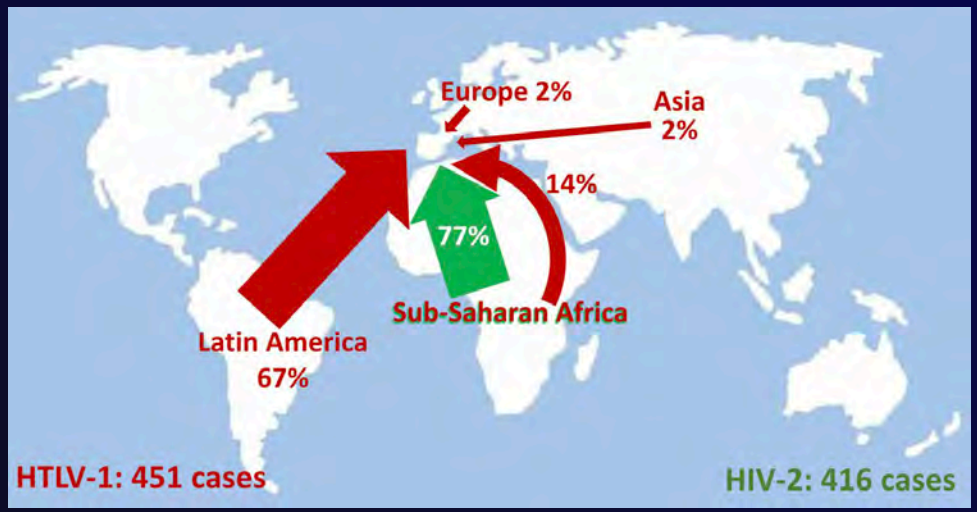


Figure 1. Yearly reported cases of HTLV-1 infection in Spain over three decades. HTLV-1; Human T-lymphotropic Virus-1



REVIEW
WILEY

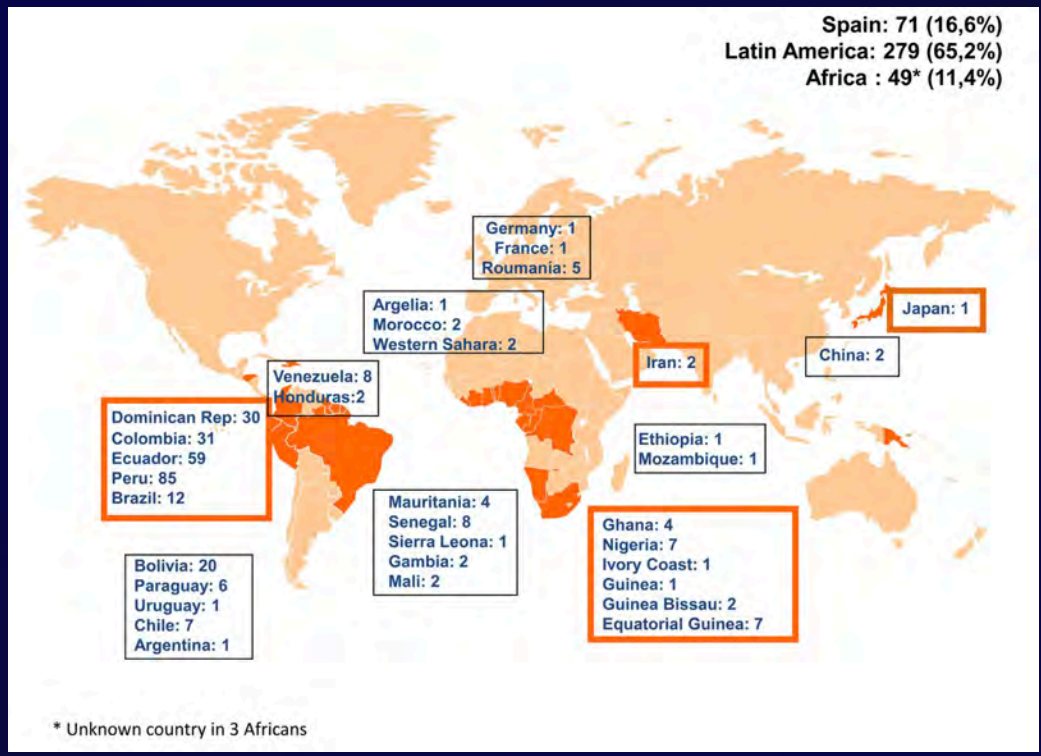
The slowdown of new infections by human retroviruses has reached a plateau in Spain

Carmen de Mendoza[1] | Paula Carrizo[1] | Silvia Sauleda[2] | Alberto Richart[3] | Ariadna Rando[4] | Elisenda Miró[5] | Rafael Benito[6] | Oscar Ayerdi[7] | Begoña Encinas[1] | Antonio Aguilera[8] | Gabriel Reina[9] | Silvia Rojo[10] | Rocío González[3] | Mario Fernández-Ruiz[11] | Paloma Liendo[12] | Natalia Montiel[13] | Lourdes Roc[14] | Ana Treviño[15] | María José Pozuelo[16] | Vicente Soriano[15] | The HTLV Spanish Network

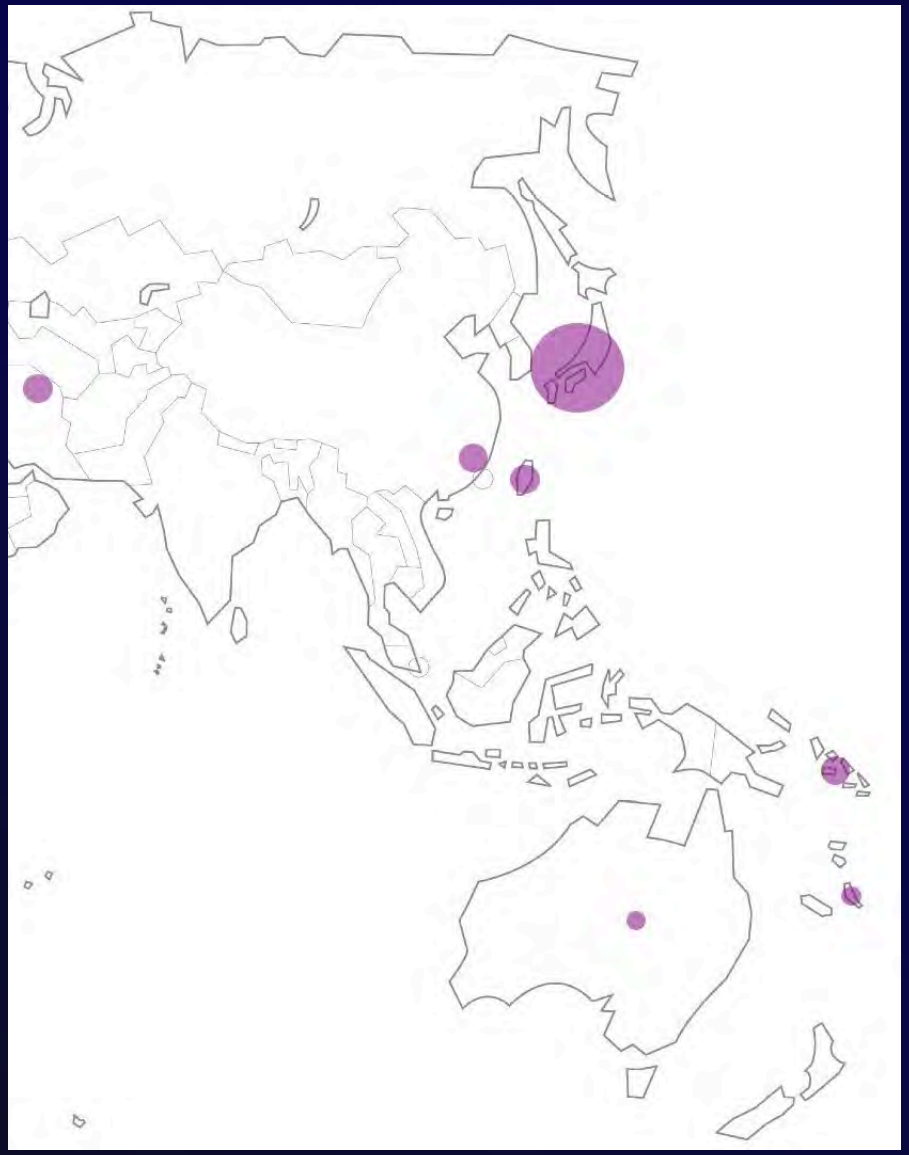
Table 1
Clinical presentationof individuals with HTLV-1 diagnosis in Spain.

	Total (n=428)	LATAM (n=280)	SSA (n=49)	NS (n=71)	LATAM vs SSA/NS (*P*)
Asymptomatic	332	223	34	48	79.6% vs 68.3% (*P* = 0.015)
Symptomatic	96	57	15	23	20.4% vs 31.7% (*P* = 0.015)
HAM/TSP	55	32	5	17	12.5% vs 21.2% (*P* = 0.04)
ATLL	33	19	8	6	7.9% vs 14.6% (*P* = 0.06)
Strongyloides stercoralis	8	6	2	0	2.6% vs 2.4% (ns)

ATLL = adult T-cell leukemia/lymphoma; HAM = HTLV-1-associated myelopathy; HTLV-1 = human T-lymphotropic virus type 1; LATAM = Latin America; NS = native Spaniards; SSA = Sub-Saharan Africa; TSP = Tropical spastic paraparesis;



Asia & Australo-Melanesia



Continent / Country	Population°	HTLV-1 range	
ASIA			
Fujian Province (China)	35 110 000	2 000	20 000
Japan*	127 368 088	1 080 000	1 300 000
Mashad area (Iran)	78 868 711	10 000	40 000
Taiwan	23 113 901	10 000	30 000
AUSTRALO-MELANESIA			
Australia (Aboriginal Australians)	463 900	2 500	5 000
Solomon Islands	584 578	3 000	6 000
Vanuatu	227 574	250	1 000

For nearly 3 billion persons (China, India,…), no reliable epidemiological data, despite the presence of small series or sporadic cases of ATLL and TSP/HAM and studies in blood donors (China +)

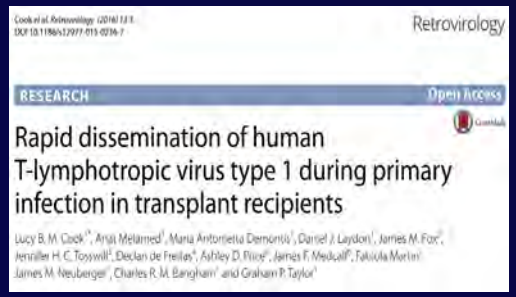
Solid organ transplantation and HTLV-1

REVIEW

WILEY

Human T-lymphotropic virus type 1 infection and solid organ transplantation

Graham P. Taylor

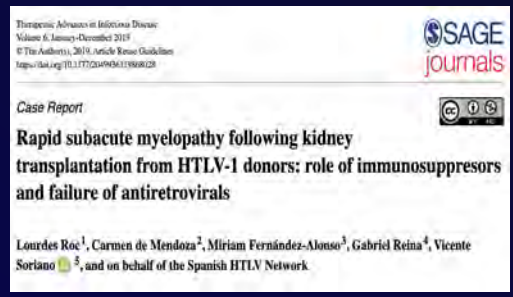


Retrovirology

RESEARCH

Open Access

Rapid dissemination of human T-lymphotropic virus type 1 during primary infection in transplant recipients



SAGE journals

Case Report

Rapid subacute myelopathy following kidney transplantation from HTLV-1 donors: role of immunosuppresors and failure of antiretrovirals

Lourdes Roc[1], Carmen de Mendoza[2], Miriam Fernández-Alonso[3], Gabriel Reina[4], Vicente Soriano[3], and on behalf of the Spanish HTLV Network

BMC Infectious Diseases

RESEARCH ARTICLE

Open Access

HTLV-1 infection in solid organ transplant donors and recipients in Spain

TABLE 2 Cases of HTLV-1-asssociated disease occurring following documented transplantation-related infection

Gender, Age (y)	Organ	Time to Onset	Disease	Progression	Treatment and Response	Ref
Male, 41	Heart (blood)	6 months	HAM	4 months paraplegic	Pulsed methyl prednisolone/oral steroids Able to walk 10 m	16
Female, 44	Liver	18 months	HAM	4 months paraplegic	No improvement with methyl prednisolone 1 g daily × 5 days plus 3 million IU interferon-α	35
Female, 53	Kidney	<2 years	HAM	Not stated		36
Male, 55	Kidney	<2 years	HAM	Not stated		36
Female	Liver	2 years	Cutaneous ATLL	Indolent	Complete remission with reduced immunosuppression	37
	Kidney	3 years	Cutaneous ATLL	Indolent	Complete remission with reduced immunosuppression	38
Female, 46	Kidney	4 years	HAM	Walking unaided after 4 years HAM	Walking unaided 6 years after onset HAM	37
Female, 38	Kidney	2 months	HAM	OMDS 5 at 4 months	Interferon Improved to OMDS 4	29
Male, 50	Kidney	4 years	HAM	Remained ambulant 2 years post onset	Not reported	30
Male, 56	Kidney	5 months	HAM	1 month wheel-chair dependent	Pulsed methyl prednisolone/oral steroids Able to walk "unaided" indoors uses frame otherwise	40
Female, 42	Kidney	3 years	HAM	Ambulant with spastic unstable gait	OMDS improved from 8 to 5 following 1 month therapy with 3 million IU interferon-α	36
Male, 65	Kidney	8 months	HAM	Wheelchair dependent within 12 days of onset	No improvement following 3 doses 1-g methyl prednisolone	36
Male	Kidney	36 months	HAM	Limited to 20 m with 1 walking stick 3 months post onset	Pulsed methyl prednisolone and increased oral steroids. Steroid dependent—normal gait 33 months post onset	Unpublished

Abbreviation: OMDS, Osame Motor Disability Scale.

Table 1 Clinical details of transplant recipients

	Case 1	Case 2	Case 3
Primary organ pathology	Alcoholic liver disease	Tubulo-interstitial nephritis with focal sclerosis	End stage renal failure of unknown aetiology (diabetes/hypertension)
Age at transplantation (years)	58	48	57
Ethnicity	Caucasian	Black Caribbean	Indian
Organ transplanted	Liver	Kidney	Kidney
Class 1 HLA type	A01, A24, B08, B15, C03, C07 DR1, DR3 DQ2, DQ5	A3, A34, B51, B71, Cw3, Cw16, DR13, DQ7	A3, A24; B52, B55; Cw1, Cw12; DR10 DR14; DQ5
Peri-operative immune suppression	Basiliximab Methylprednisolone	Basiliximab Methylprednisolone	Basiliximab Mycophenolate, Tacrolimus
Post operative immune suppression	Mycophenolate, tacrolimus	None	Tacrolimus, prednisolone
Day post transplant antiretrovirals commenced	Day 19	Day 17	Day 26
Dose of antiretrovirals	Zidovudine 250 mg bd Raltegravir 400 mg bd	Zidovudine 100 mg tds Raltegravir 400 mg bd	Zidovudine 100 mg tds Raltegravir 400 mg bd
Day antiretrovirals stopped	Day 66	Day 43	Day 80
Day organ removed	Not applicable	Day 0	Day 48
Indication for organ removal	Not applicable	Life-threatening intra-operative haemorrhage	Rejection/failure

b.d. *Bis in die* (twice a day), t.d.s. *ter die sumendum* (three times daily)

	Country	Year	Age (years)	Gender	Organ	Interval	Reference
HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP)							
1	France	1990	41	Male	Heart	5 months	Gout *et al.*[13]
2	Japan	1992	32	Male	Kidney	11 months	Kuroda *et al.*[14]
3	Japan	2000	50	Male	Kidney	4 years	Nakatsuji *et al.*[15]
4	Spain	2003	44	Female	Liver	18 months	Toro *et al.*[16]
5	Spain	2003	54	Female	Kidney	<3 months	Toro *et al.*[16]
6	Spain	2003	57	Male	Kidney	20 months	Toro *et al.*[16]
7	Japan	2008	58	Male	Liver	20 months	Soyama *et al.*[17]
8	Japan	2010	51	Male	Kidney	10 months	Inose *et al.*[18]
9	USA	2014	56	Male	Kidney	5 months	Ramanan *et al.*[19]
10	USA	2015	59	Female	Kidney	8 years	Younger[20]
11	Germany	2016	46	Female	Kidney	4 years	Gövert *et al.*[21]
12	Japan	2015	38	Female	Kidney	2 months	Nagamine *et al.*[22]
13	Japan	2016	42	Female	Kidney	3 years	Tajima *et al.*[23]
14	Japan	2016	65	Male	Kidney	8 months	Tajima *et al.*[23]
15	Japan	2016	?	?	Liver	15 months	Yoshizumi *et al.*[24]
16	Japan	2016	?	?	Liver	46 months	Yoshizumi *et al.*[24]
17	Ecuador	2016	40	Male	Kidney	2 years	Montesdeoca *et al.*[25]
18	Spain	2016	54	Female	Kidney	8 months	Current case

What is the situation of HTLV-1 in Africa?

Remains poorly known

Report commissioned in 2014 by the ECDC, coordinated by Dragoslav Domanović and produced by Antoine Gessain and Olivier Cassar (EPVO Unit, Institut Pasteur)

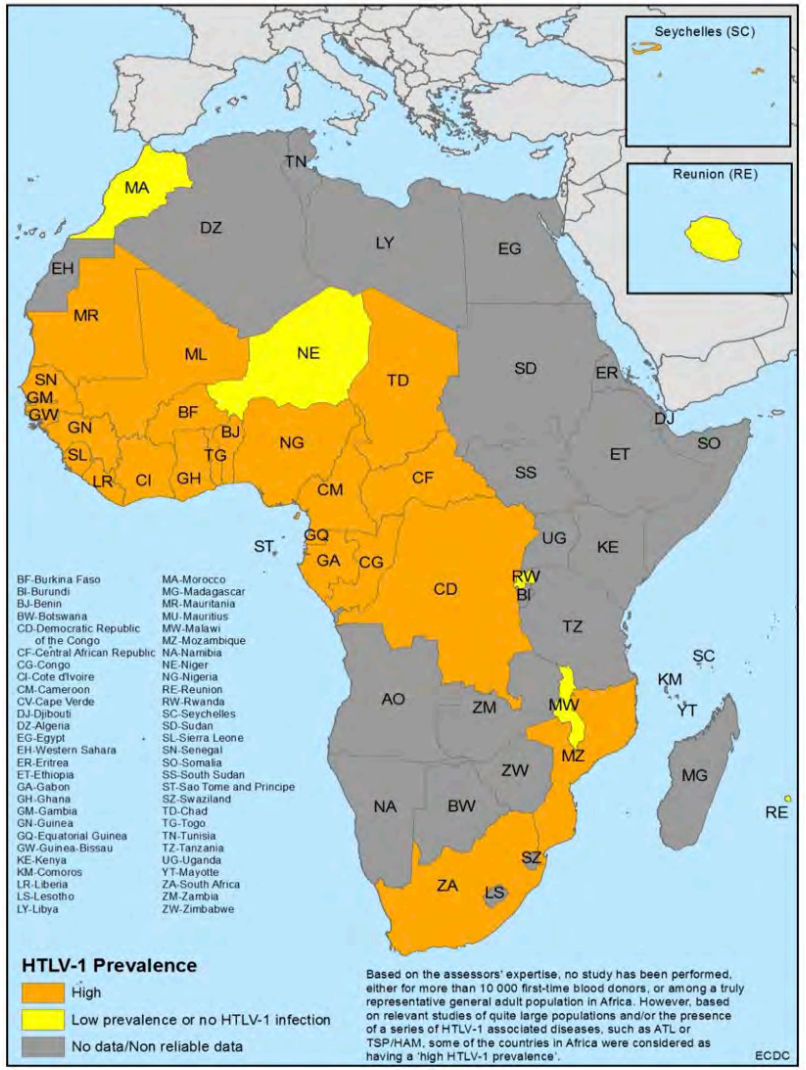
'high prevalence' – a prevalence over 1% in the general adult population or prevalence of over 1/10 000 among first-time blood donors;

'low prevalence' – a prevalence below 1% in the general adult population or prevalence of below 1/10 000 among first-time blood donors.

- WHO HTLV-1 Technical Report, 2020

- Legrand et al. Clin. Microbio. Review, 2022

Figure 4. HTLV-1 prevalence in sovereign states and territories of Africa[4]



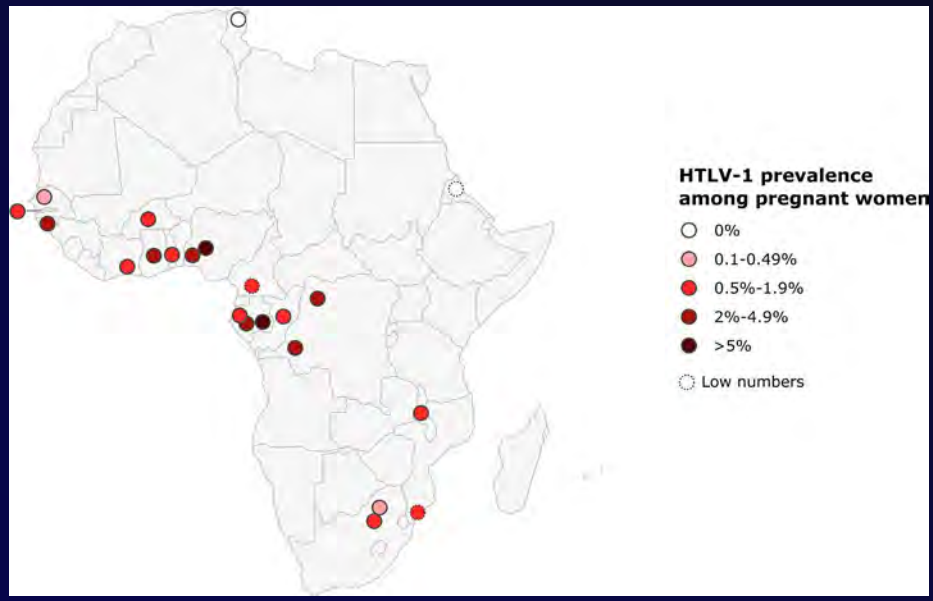
frontiers | Frontiers in Immunology
TYPE Review
PUBLISHED 03 February 2023
DOI 10.3389/fimmu.2023.1043600

Geographic distribution, clinical epidemiology and genetic diversity of the human oncogenic retrovirus HTLV-1 in Africa, the world's largest endemic area

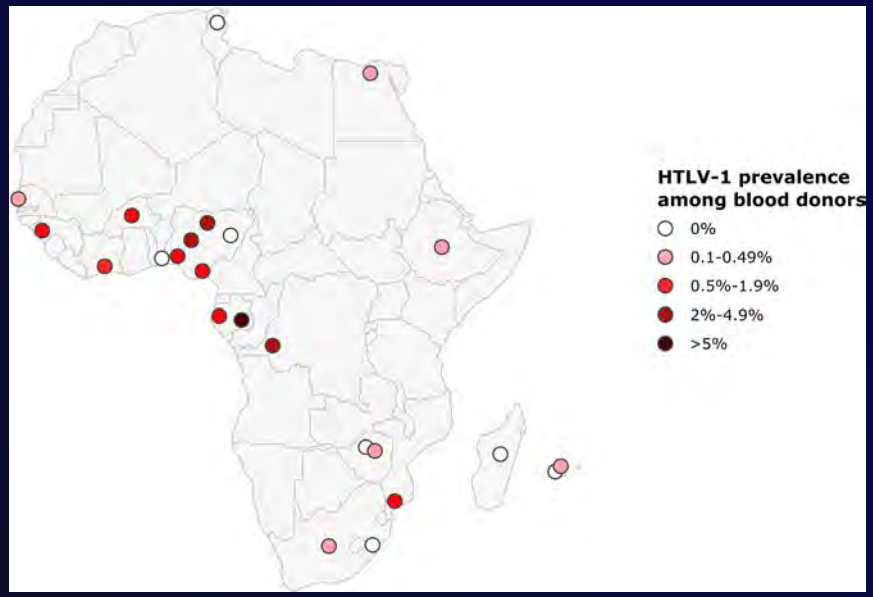
Antoine Gessain*, Jill-Léa Ramassamy, Philippe V. Afonso and Olivier Cassar*

Institut Pasteur, Université Paris Cité, CNRS UMR 3569, Unité d'Epidémiologie et Physiopathologie des Virus Oncogènes, Paris, France

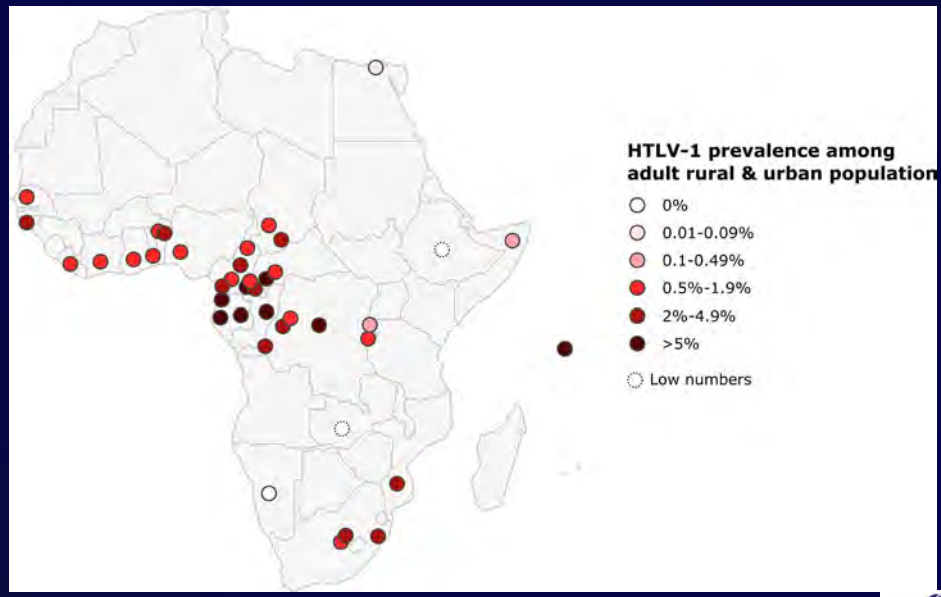
HTLV-1 prevalence in pregnant women



HTLV-1 prevalence in blood donors



HTLV-1 prevalence in adult population



Very probably the largest HTLV-1 endemic area in the world (>2.5-5.5 millions)

Continent / Country	Population°	HTLV-1 range	
AFRICA			
Senegal	12 969 606	30 000	105 000
Gambia	1 840 454	2 500	13 000
Guinea Bissau	1 628 603	12 000	28 000
Guinea	10 884 958	75 000	150 000
Sierra Leone/Liberia	5 485 998 / 3 887 886	50 000	100 000
Côte d'Ivoire	21 952 093	130 000	250 000
Ghana	25 241 998	125 000	375 000
Togo / Benin	6 961 049 / 9 598 787	80 000	160 000
Burkina Fasso	17 275 115	42 000	125 000
Mali	14 533 511	32 000	95 000
Nigeria	170 123 740	850 000	1 700 000
Cameroon	20 129 878	80 000	180 000
Equatorial Guinea	685 991	1 500	4 500
Gabon	1 608 321	16 000	30 000
Central African Republic	5 057 208	15 000	30 000
DRC	73 599 190	600 000	1 300 000
Republic of The Congo	4 366 266	12 000	36 000
Mozambique	23 515 934	120 000	360 000
South Africa	48 810 427	180 000	540 000

No reliable estimation for the highly populated areas of North and East Africa.

Need large epidemiological surveys in Nigeria, DRC,

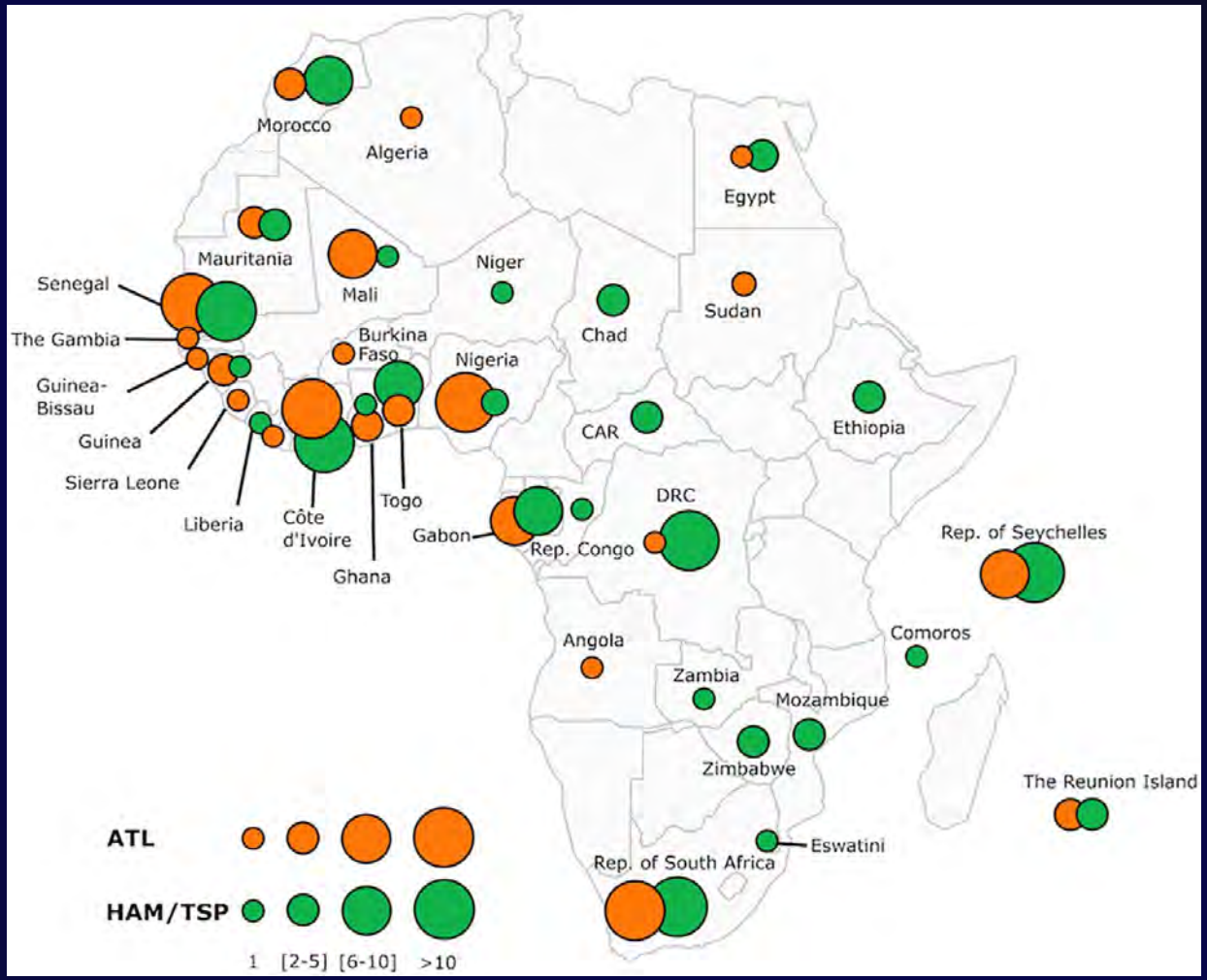
East and North Africa (> half of African population)

General distribution of ATL and HAM/TSP cases reported on the African continent and in certain Indian Ocean islands

Very few studies have been carried out *in situ*, by local MDs and ATLL has been described only very rarely in Africa (< 80 cases).

Estimates range from at least 500 to 2,500 cases/year

Local situation on the clinico-/epidemiological aspects of ATL and ID and, to a lesser extent, HAM/TSP remains virtually unknown in most parts of Africa.



160 cases of ATL/40 years

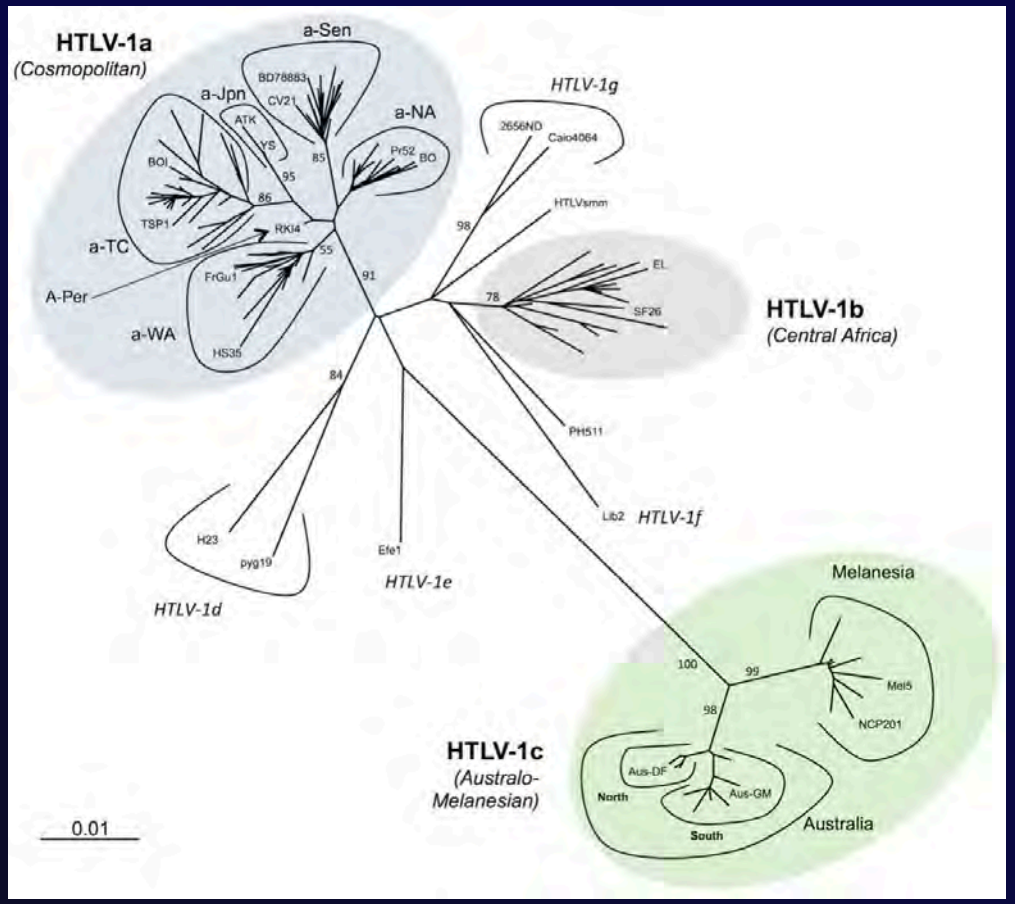
360 cases of HAM/TSP/40 years

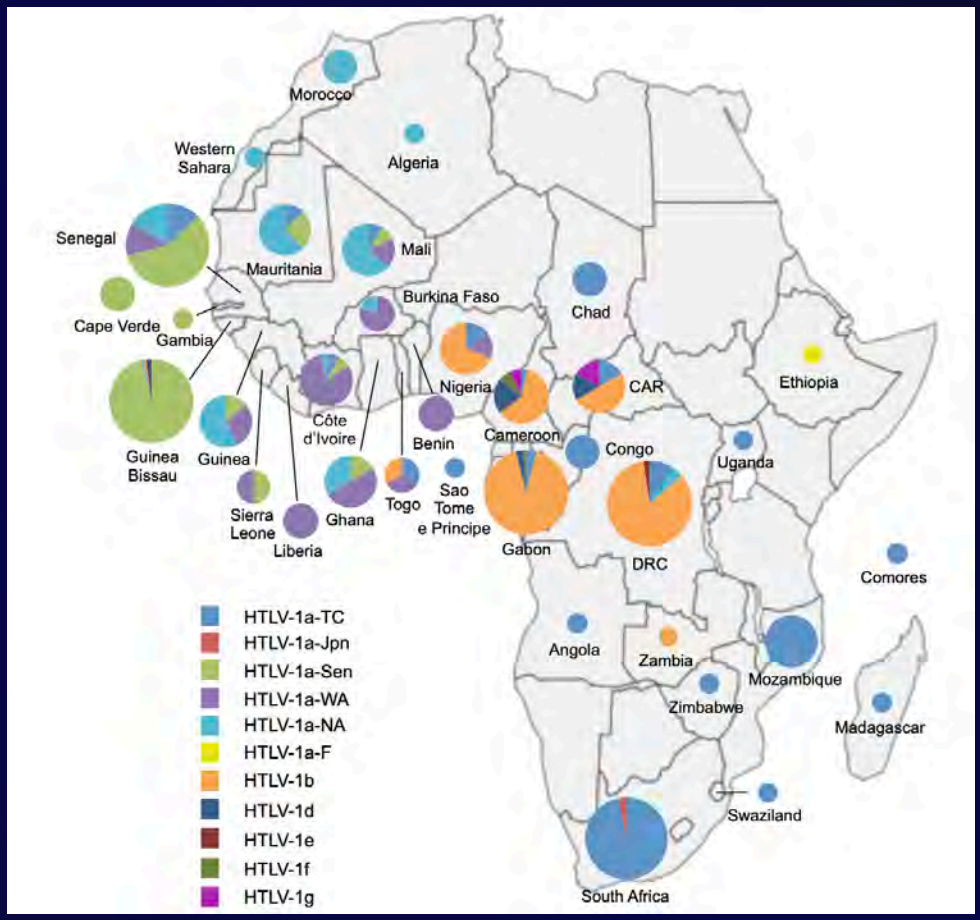
Huge under-reporting (factor >100)

Distribution of the HTLV-1 Genotypes across the African Continent

HLTV-1-a Cosmopolitan genotype with five clades a-WA, a-Sen, a-Na, a-TC and a G-Rec

In central Africa different genotypes (b, d, e, f, g) with b predominant





Afonso, Cassar, Gessain. Retrovirology, 2019

What are the predominant modes of HTLV-1 acquisition in Central Africa?

These data are crucial for public health actions

aimed to reduce the incidence of HTLV-1 infection

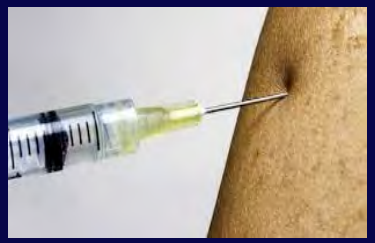
In Central Africa, there are at least six different modes of acquisition/transmission:

Mother-to-child

Sexual

Transfusion

Use of unsterile syringes,…



Scarification

Contact with fluids from NHPs

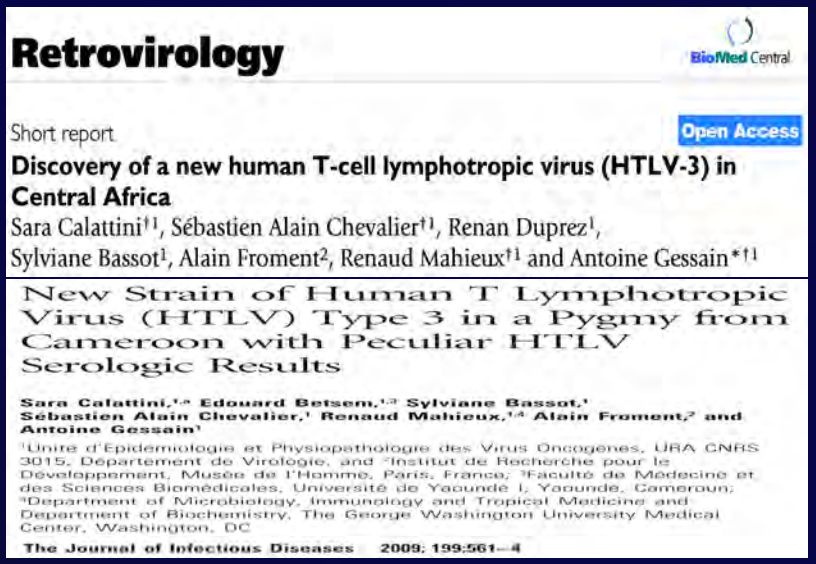
The relative contribution of each of the different HTLV-1/STLV-1 transmission routes (between the different inter-humans modes and inter-humans *vs* inter-species/NHP-Humans) remains unknown

First study in Cameroon on the origin and interspecies transmission of different retroviruses from NHPs living in the wild

More than 5000 plasmas and buffy-coats of adults (mean age 50 years) were tested in a retrospective study in general rural population including Pygmees or Bantus living close to NHPs habitats and in a prospective study focused on more than 300 individuals who reported direct contacts (bites, wounds,..) with animals, especially NHPs, mainly during hunting activities.




STLV-3/HTLV-3



Retrovirology

BioMed Central

Short report

Open Access

Discovery of a new human T-cell lymphotropic virus (HTLV-3) in Central Africa

Sara Calattini[†1], Sébastien Alain Chevalier[†1], Renan Duprez[1], Sylviane Bassot[1], Alain Froment[2], Renaud Mahieux[†1] and Antoine Gessain[*†1]

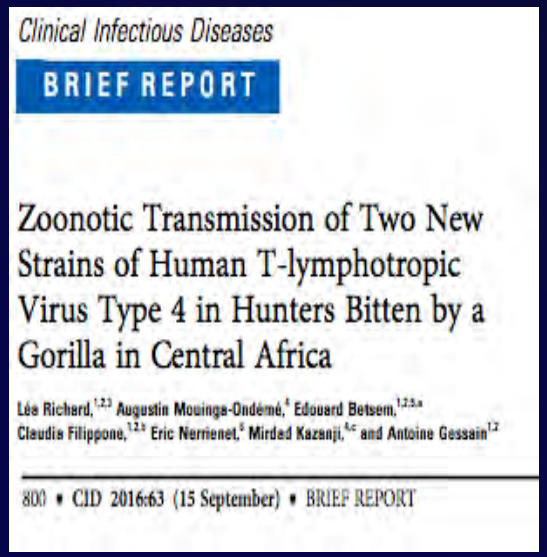
New Strain of Human T Lymphotropic Virus (HTLV) Type 3 in a Pygmy from Cameroon with Peculiar HTLV Serologic Results

Sara Calattini,[1,a] Edouard Betsem,[1,3] Sylviane Bassot,[1] Sébastien Alain Chevalier,[1] Renaud Mahieux,[1,4] Alain Froment,[2] and Antoine Gessain[1]

[1]Unité d'Epidémiologie et Physiopathologie des Virus Oncogènes, URA CNRS 3015, Département de Virologie, and [2]Institut de Recherche pour le Développement, Musée de l'Homme, Paris, France; [3]Faculté de Médecine et des Sciences Biomédicales, Université de Yaoundé I, Yaoundé, Cameroun; [4]Department of Microbiology, Immunology and Tropical Medicine and Department of Biochemistry, The George Washington University Medical Center, Washington, DC

The Journal of Infectious Diseases 2009; 199:561–4

STLV-4/HTLV-4



Clinical Infectious Diseases

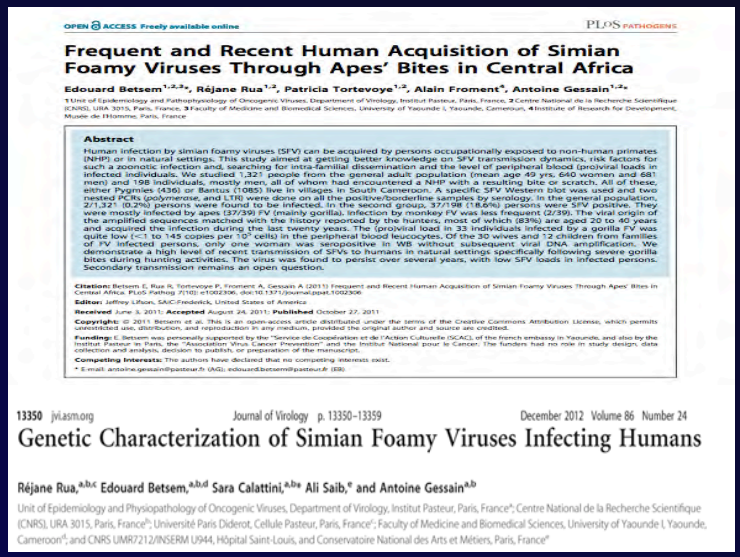
BRIEF REPORT

Zoonotic Transmission of Two New Strains of Human T-lymphotropic Virus Type 4 in Hunters Bitten by a Gorilla in Central Africa

Léa Richard,[1,2,3] Augustin Mouinga-Ondémé,[4] Edouard Betsem,[1,2,3,a] Claudia Filippone,[1,2,3] Eric Nerrienet,[5] Mirdad Kazanji,[4,c] and Antoine Gessain[1,2]

800 • CID 2016:63 (15 September) • BRIEF REPORT

Simian Foamy Viruses



OPEN ACCESS Freely available online PLOS PATHOGENS

Frequent and Recent Human Acquisition of Simian Foamy Viruses Through Apes' Bites in Central Africa

Edouard Betsem[1,2,3]*, Réjane Rua[1,2], Patricia Tortevoye[1,2], Alain Froment[4], Antoine Gessain[1,2]*

[1] Unit of Epidemiology and Pathophysiology of Oncogenic Viruses, Department of Virology, Institut Pasteur, Paris, France, [2] Centre National de la Recherche Scientifique (CNRS), URA 3015, Paris, France, [3] Faculty of Medicine and Biomedical Sciences, University of Yaounde I, Yaounde, Cameroun, [4] Institute of Research for Development, Musée de l'Homme, Paris, France

Abstract

Human infection by simian foamy viruses (SFV) can be acquired by persons occupationally exposed to non-human primates (NHP) or in natural settings. This study aimed at getting better knowledge on SFV transmission dynamics, risk factors for such a zoonotic infection and, searching for intra-familial dissemination and the level of peripheral blood (provirial loads in infected individuals. We studied 1,321 people from the general adult population (mean age 49 yrs, 640 women and 681 men) and 198 individuals, mostly men, all of whom had encountered a NHP with a resulting bite or scratch. All of these, either Pygmies (436) or Bantus (1085) live in villages in South Cameroon. A specific SFV Western blot was used and two nested PCRs (polymerase, and LTR) were done on all the positive/borderline samples by serology. In the general population, 2/1,321 (0.2%) persons were found to be infected. In the second group, 37/198 (18.6%) persons were SFV positive. They were mostly infected by apes (37/39) FV (mainly gorilla). Infection by monkey FV was less frequent (2/39). The viral origin of the amplified sequences matched with the history reported by the hunters, most of which (83%) are aged 20 to 40 years and acquired the infection during the last twenty years. The (provirial load in 33 individuals infected by a gorilla FV was quite low (<1 to 145 copies per 10^5 cells) in the peripheral blood leucocytes. Of the 30 wives and 12 children from families of FV infected persons, only one woman was seropositive in WB without subsequent viral DNA amplification. We demonstrate a high level of recent transmission of SFVs to humans in natural settings specifically following severe gorilla bites during hunting activities. The virus was found to persist over several years, with low SFV loads in infected persons. Secondary transmission remains an open question.

Citation: Betsem E, Rua R, Tortevoye P, Froment A, Gessain A (2011) Frequent and Recent Human Acquisition of Simian Foamy Viruses Through Apes' Bites in Central Africa. PLoS Pathog 7(10): e1002306. doi:10.1371/journal.ppat.1002306

Editor: Jeffrey Lifson, SAIC-Frederick, United States of America

Received June 3, 2011; **Accepted** August 24, 2011; **Published** October 27, 2011

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Funding: E. Betsem was personally supported by the "Service de Coopération et de l'Action Culturelle (SCAC), of the french embassy in Yaounde, and also by the Institut Pasteur in Paris, the "Association Virus Cancer Prevention" and the Institut National pour le Cancer. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

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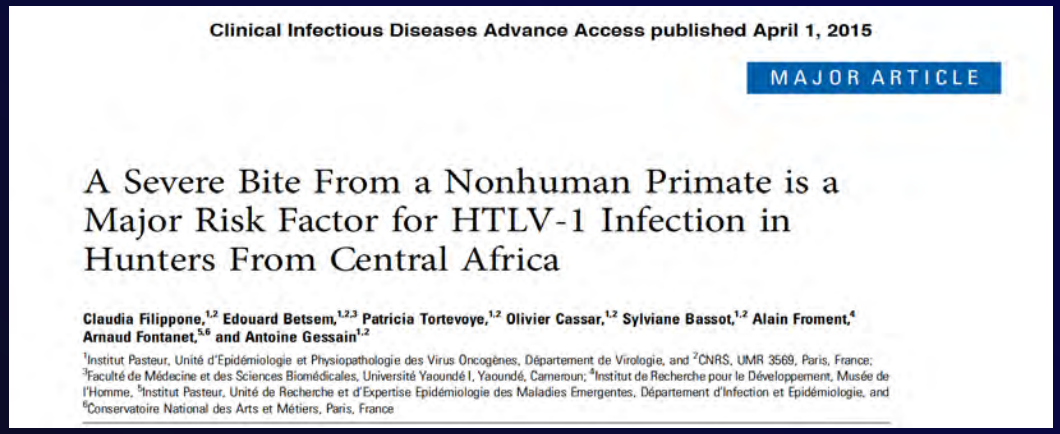
13350 jvi.asm.org Journal of Virology p. 13350–13359 December 2012 Volume 86 Number 24

Genetic Characterization of Simian Foamy Viruses Infecting Humans

Réjane Rua,[a,b,c] Edouard Betsem,[a,b,d] Sara Calattini,[a,b,e] Ali Saib,[e] and Antoine Gessain[a,b]

Unit of Epidemiology and Physiopathology of Oncogenic Viruses, Department of Virology, Institut Pasteur, Paris, France[a]; Centre National de la Recherche Scientifique (CNRS), URA 3015, Paris, France[b]; Université Paris Diderot, Cellule Pasteur, Paris, France[c]; Faculty of Medicine and Biomedical Sciences, University of Yaounde I, Yaounde, Cameroon[d]; and CNRS UMR7212/INSERM U944, Hôpital Saint-Louis, and Conservatoire National des Arts et Métiers, Paris, France[e]

STLV-1/HTLV-1



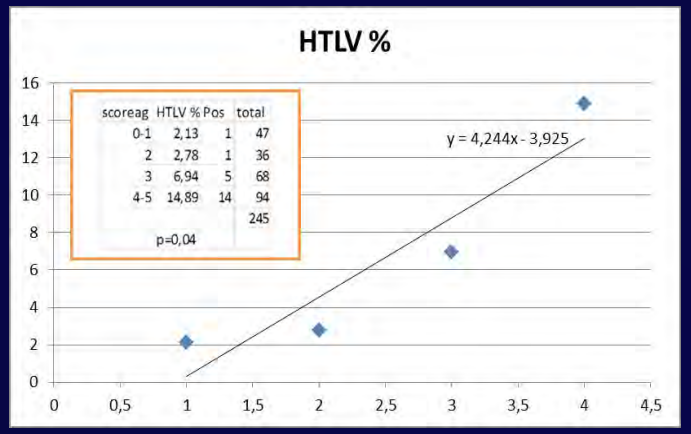
Clinical Infectious Diseases Advance Access published April 1, 2015

MAJOR ARTICLE

A Severe Bite From a Nonhuman Primate is a Major Risk Factor for HTLV-1 Infection in Hunters From Central Africa

Claudia Filippone,[1,2] Edouard Betsem,[1,2,3] Patricia Tortevoye,[1,2] Olivier Cassar,[1,2] Sylviane Bassot,[1,2] Alain Froment,[4] Arnaud Fontanet,[5,6] and Antoine Gessain[1,2]

[1]Institut Pasteur, Unité d'Epidémiologie et Physiopathologie des Virus Oncogènes, Département de Virologie, and [2]CNRS, UMR 3569, Paris, France; [3]Faculté de Médecine et des Sciences Biomédicales, Université Yaoundé I, Yaoundé, Cameroun; [4]Institut de Recherche pour le Développement, Musée de l'Homme, [5]Institut Pasteur, Unité de Recherche et d'Expertise Epidémiologie des Maladies Emergentes, Département d'Infection et Epidémiologie, and [6]Conservatoire National des Arts et Métiers, Paris, France



HTLV-1 infection was associated to the severity of the bite

Epidémiologie et Physiopathologie des Virus Oncogènes

INSTITUT PASTEUR

Blood Donors Survey in Libreville, Gabon

DONOR INFECTIOUS DISEASE TESTING

High prevalence of human T-cell leukemia virus type-1b genotype among blood donors in Gabon, Central Africa

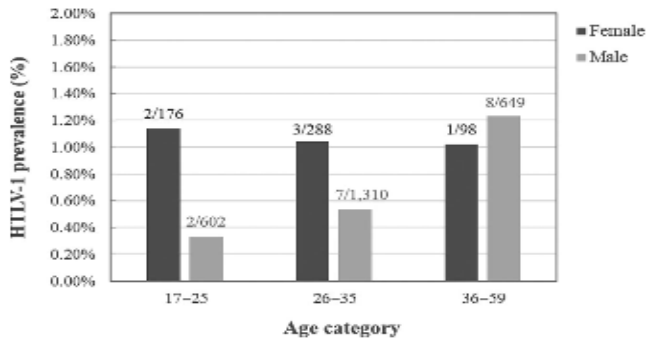
Jill-Léa Ramassamy,[1,2] Olivier Cassar,[1] Manoushka Toumbiri,[3] Abdoulaye Diané,[3] Antony Idam Mamimandjiami,[1,3,4] Calixte Bengone,[5] Jophrette Mireille Ntsame-Ndong,[5] Augustin Mouinga-Ondémé,[3,1] and Antoine Gessain[1]

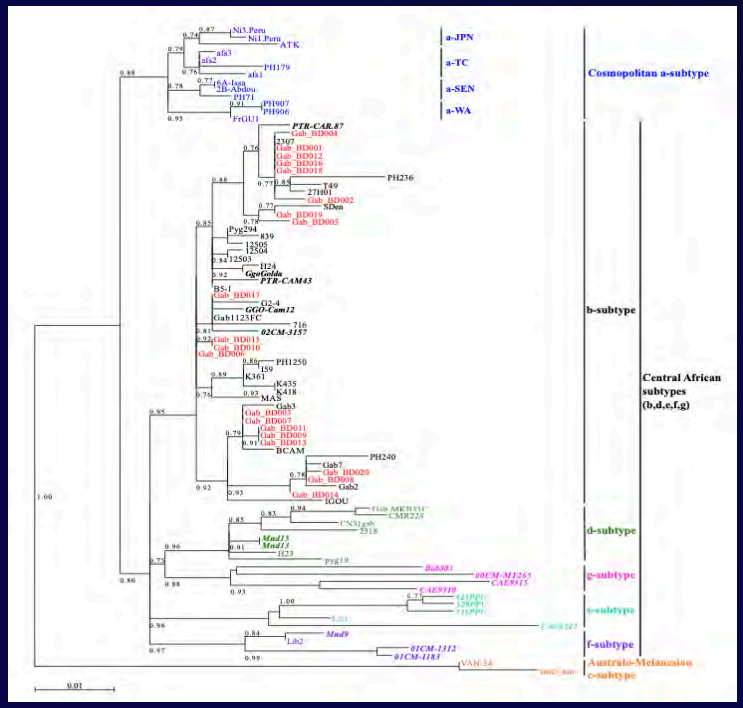
Volume 60, July 2020 TRANSFUSION 1483

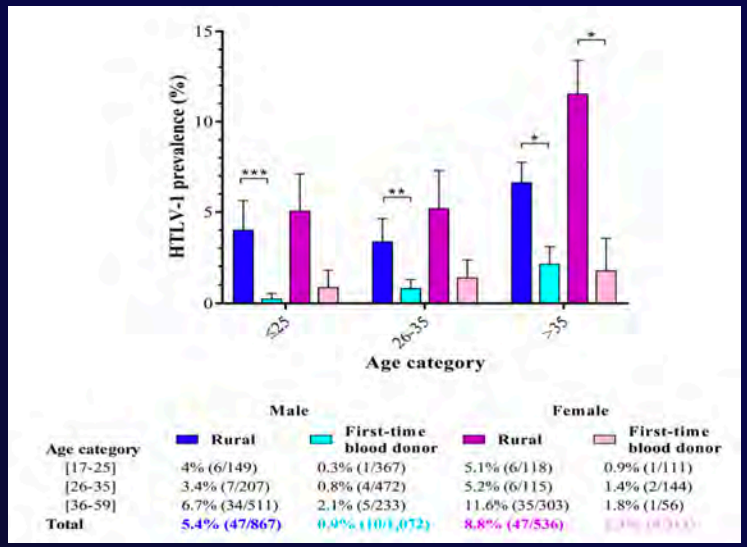
TABLE 1. Prevalence of HTLV-1 according to demographic characteristics and donor status

	n+/N	HTLV-1 prevalence (95% CI)	Crude OR (95% CI)	p value
Sex				
M	17/2561	0.7% (0.4-1.1)	1	0.31
F	6/562	1.1% (0.4-2.3)	1.03 (0.6-4.1)	
Age (years)				
17-25	4/778	0.5% (0.1-1.3)	1	0.22
26-35	10/1598	0.6% (0.3-1.1)	1.22 (0.4-3.9)	
36-59	9/747	1.2% (0.6-2.3)	2.36 (0.7-7.7)	
History of blood donation				
Repeat	9/1740	0.5% (0.2-1)	1	0.11
First-time	14/1378	1.0% (0.6-1.7)	1.97 (0.9-4.6)	
Unknown	0/5	0% (0-52)*	-	-
Type of blood donor				
Volunteer	5/1083	0.5% (0.2-1.1)	1	0.17
Familial	16/1941	0.8% (0.5-1.3)	1.79 (0.7-4.9)	
Unknown	2/99	2.0% (0.2-7.1)	4.45 (0.9-23.2)	
Total	**23/3123**	**0.7% (0.5-1.1)**		

* One-sided 97.5% confidence interval.
n+ = number of HTLV-1 infected individuals; N total number of individuals tested.







Age category	Male: Rural	Male: First-time blood donor	Female: Rural	Female: First-time blood donor
[17-25]	4% (6/149)	0.3% (1/367)	5.1% (6/118)	0.9% (1/111)
[26-35]	3.4% (7/207)	0.8% (4/472)	5.2% (6/115)	1.4% (2/144)
[36-59]	6.7% (34/511)	2.1% (5/233)	11.6% (35/303)	1.8% (1/56)
Total	5.4% (47/867)	0.9% (10/1,072)	8.8% (47/536)	[illegible]

Overall prevalence of 0,74 % (23/3123),1% in FTBD and 0,5 % in repeat donors

Age and sex-adjusted prevalence was five fold lower in FTBD that in the general adult population of rural areas

Received: 11 May 2023 | Accepted: 06 July 2023
DOI: 10.1111/bjh.18988

LETTER TO THE EDITOR

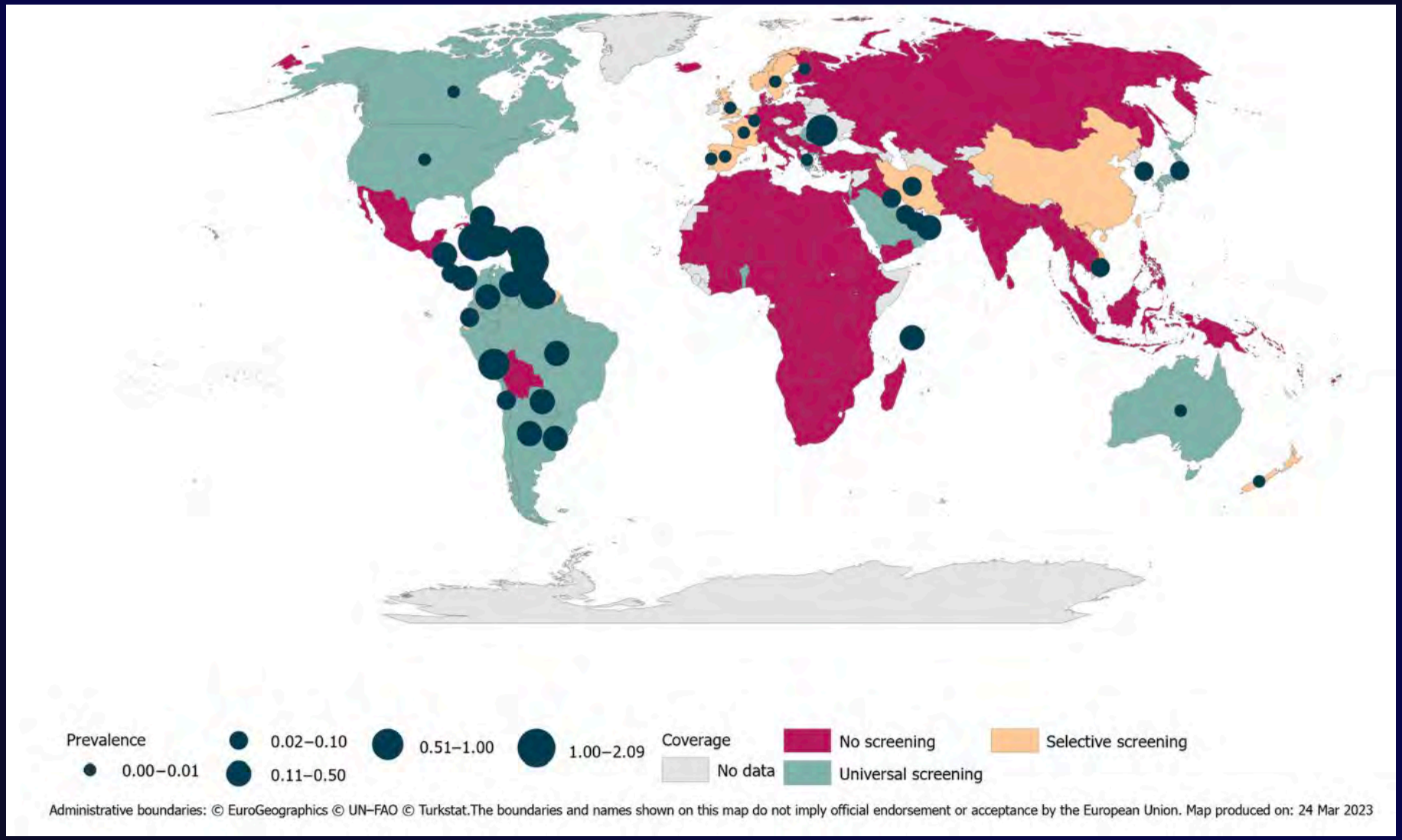
BJHaem

HTLV-1 screening of blood donations: We are systematically missing opportunities

Carolina Rosadas[1]
Heli Harvala[2]
Katy Davison[3]
Graham P. Taylor[1,4]

Screening tests +/- confirmation assays ?
Depends on the country

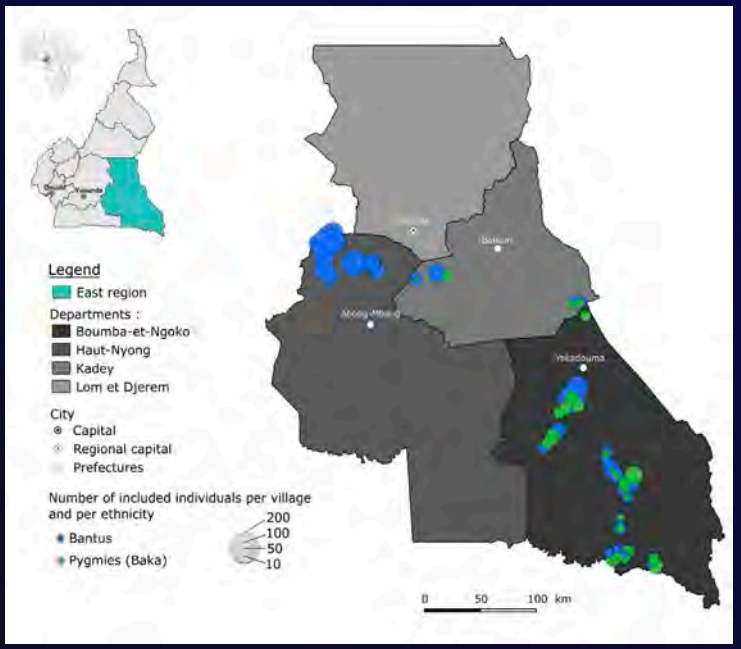
The more there are, the less we test
the fewer there are, the more we test

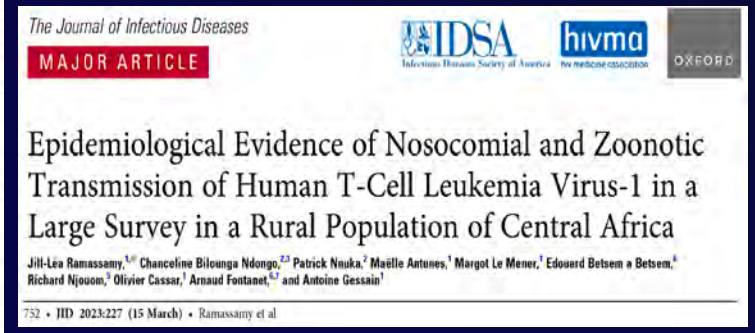


Large Rural Population-based Survey In South Cameroon

Variables	aOR	95% CI	*P* Value
Ethnic group			
Bantu	1	…	…
Pygmy	2.9	1.3–6.2	.007**
History of hospitalization and surgery			
Never hospitalized	1	…	.002**
Hospitalization without surgery	2.4	.9–6.2	…
Hospitalization with history of surgery	6.3	2.2–17.8	…
Bitten by an NHP			
No	1	…	…
Yes	6.6	2.2–19.8	.001**

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval. **$P < .01$.



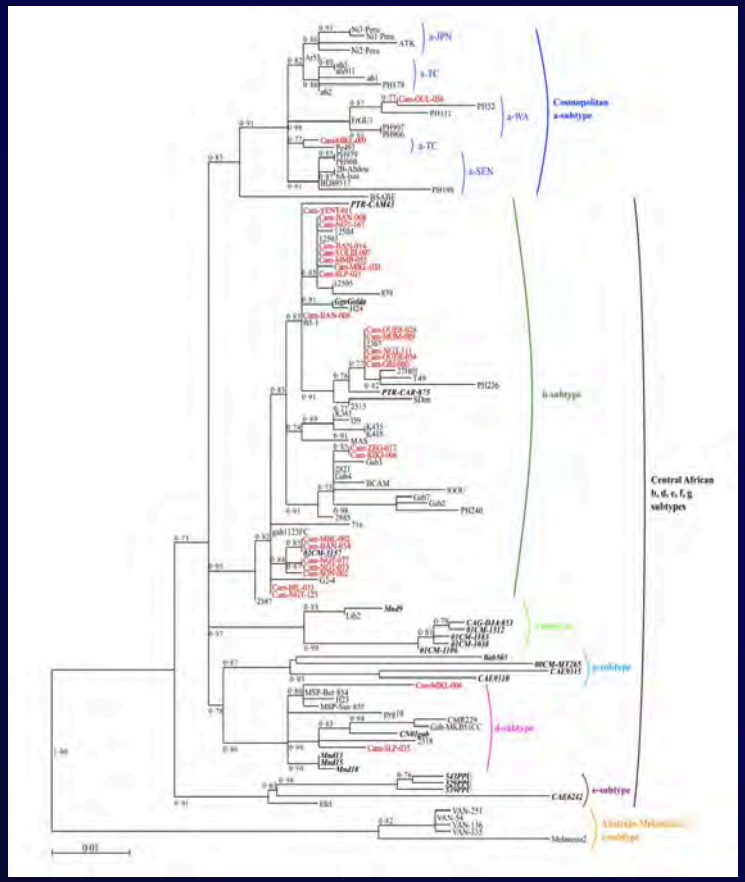

The Journal of Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America · hivma hiv medicine association · OXFORD

Epidemiological Evidence of Nosocomial and Zoonotic Transmission of Human T-Cell Leukemia Virus-1 in a Large Survey in a Rural Population of Central Africa

Jill-Léa Ramassamy,[1,a] Chanceline Bilounga Ndongo,[2,3] Patrick Nauka,[2] Maëlle Antunes,[1] Margot Le Mener,[1] Edouard Betsem a Betsem,[4] Richard Njouom,[2] Olivier Cassar,[1] Arnaud Fontanet,[4,5] and Antoine Gessain[1]



Overall prevalence of 1.1 % in adult rural population (36/3400) with a distribution heterogenous in the area.

Factors independently associated with HTLV-1 were Pygmy ethnicity, history of surgery and a NHP bite.

All detected strains belong to HTLV-1 b genotype but were highly diverse

A new large ongoing study is ongoing in blood donnors from Cameroon

Take-Home Messages

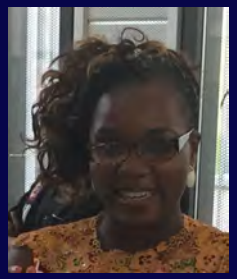
1) The actual geographical distribution of HTLV-1 and the number of HTLV-1 infected individuals remain largely unknown: large-scale epidemiological surveys are needed in North and East Africa, as well as in Asia (India, China, etc.).

2) Modes of transmission are well known: Sexual transmission mainly from male to women (IST WHO), Mother-to-child transmission mainly linked to prolonged breastfeeding, Contaminated blood products (cell-associated virus), during organ transplantation, in a religious/ritual context, Zoonotic transmission.

3) In Africa, the largest HTLV-1 endemic area, there is a diversity of transmission routes that vary from region to region, but their relative contribution remains unknown and **there are no public health measures implemented to reduce the transmission and dissemination of this oncogenic retrovirus.**

Acknowledgments

Institut Pasteur



Djuicy D

Ramassamy JL

IRD/MNHN, Orléans/Paris

Alain Froment

Buseyne F

Filippone C

Afonso P V

Tortevoye P

Cassar O

Gessain A

Field mission, South Cameroon, Pygmy Settlement

Université Médicale du Cameroun Yaoundé

Edouard Betsem

CIRMF, Franceville,Gabon

Augustin Mouinga Ondeme

CPC yaoundé,

Richard Njouom

Epidémiologie des maladies émergentes

Arnaud Fontanet

Epidémiologie et Physiopathologie des Virus Oncogènes

Screening of donors for HTLV-1

Sharing of experience- testing of donors in Spain

Beatriz Mahillo
bmahillo@sanidad.gob.es

Organ Transplantation risks

RISKS ATTRIBUTABLE TO INCIDENTS DURING THE DONATION AND TRANSPLANTATION PROCESS

IDENTIFICATION → EVALUATION/ SELECTION → PROCUREMENT → PRESERVATION/ TRANSPORT → TRANSPLANT

RISKS INHERENT TO TRANSFER OF BIOLOGICAL MATERIAL BETWEEN INDIVIDUALS

(never risk 0)

RISKS ARE OFTEN SHARED BY DIFFERENT TEAMS PHYSICALLY LOCATED DISTANT FROM EACH OTHER

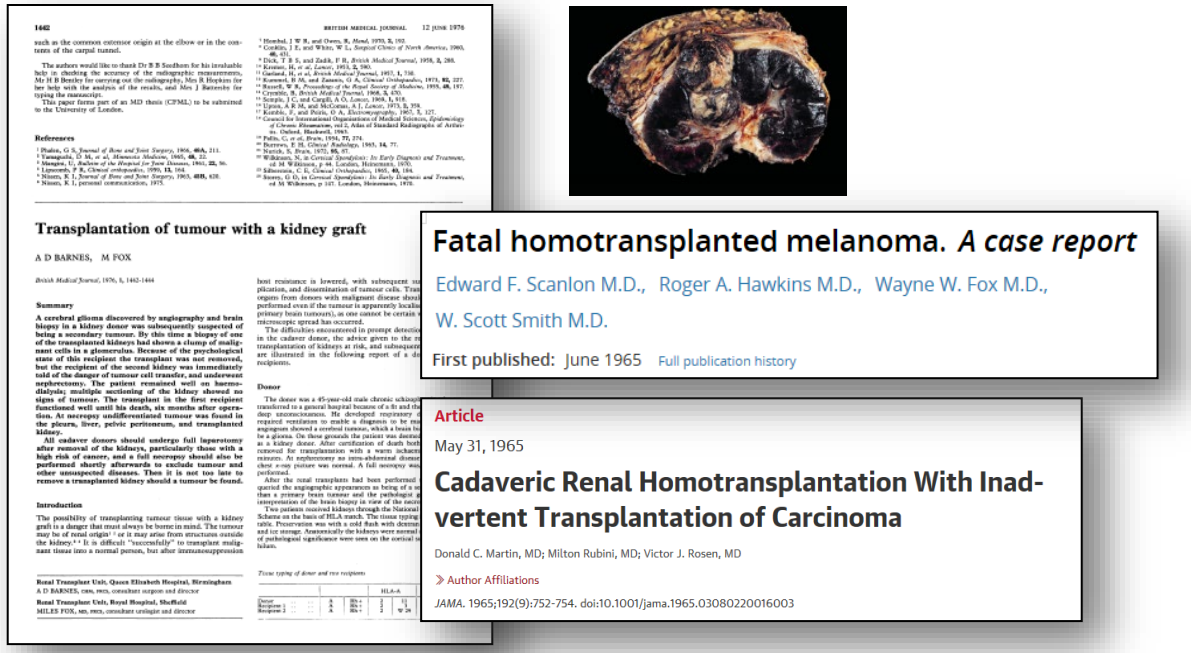
RISKS FREQUENTLY ASSUMED

LIMITATIONS OF DONOR HISTORY (MEDICAL, SOCIAL AND BEHAVIOURAL DATA)
DONOR HISTORY FROM RELATIVES

Coordination

Preventable Errors in Organ Transplantation: An Emerging Patient Safety Issue
Ison et al. Am J Transplant. 2012

The risk of disease transmission from donors is known since the early days of clinical transplantation



Transplantation of tumour with a kidney graft

A D BARNES, M FOX

Fatal homotransplanted melanoma. *A case report*

Edward F. Scanlon M.D., Roger A. Hawkins M.D., Wayne W. Fox M.D., W. Scott Smith M.D.

First published: June 1965 Full publication history

Article

May 31, 1965

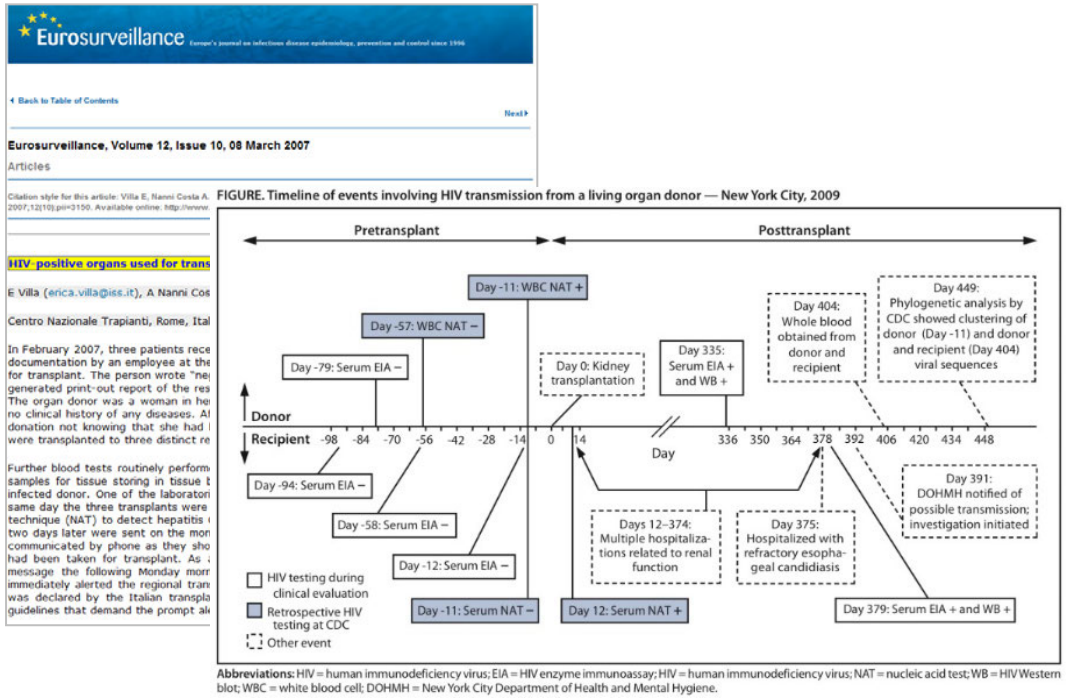
Cadaveric Renal Homotransplantation With Inadvertent Transplantation of Carcinoma

Donald C. Martin, MD; Milton Rubini, MD; Victor J. Rosen, MD

Author Affiliations

JAMA. 1965;192(9):752-754. doi:10.1001/jama.1965.03080220016003

Cancer



Eurosurveillance

Eurosurveillance, Volume 12, Issue 10, 08 March 2007

Articles

FIGURE. Timeline of events involving HIV transmission from a living organ donor — New York City, 2009

Pretransplant

Posttransplant

Donor

Recipient -98 -84 -70 -56 -42 -28 -14 0 14 Day 336 350 364 378 392 406 420 434 448

Day -11: WBC NAT +

Day -57: WBC NAT –

Day -79: Serum EIA –

Day 0: Kidney transplantation

Day 335: Serum EIA + and WB +

Day 404: Whole blood obtained from donor and recipient

Day 449: Phylogenetic analysis by CDC showed clustering of donor (Day -11) and donor and recipient (Day 404) viral sequences

Day -94: Serum EIA –

Day -58: Serum EIA –

Day -12: Serum EIA –

Day -11: Serum NAT –

Day 12: Serum NAT +

Days 12–374: Multiple hospitalizations related to renal function

Day 375: Hospitalized with refractory esophageal candidiasis

Day 391: DOHMH notified of possible transmission; investigation initiated

Day 379: Serum EIA + and WB +

HIV testing during clinical evaluation

Retrospective HIV testing at CDC

Other event

Abbreviations: HIV = human immunodeficiency virus; EIA = HIV enzyme immunoassay; HIV = human immunodeficiency virus; NAT = nucleic acid test; WB = HIV Western blot; WBC = white blood cell; DOHMH = New York City Department of Health and Mental Hygiene.

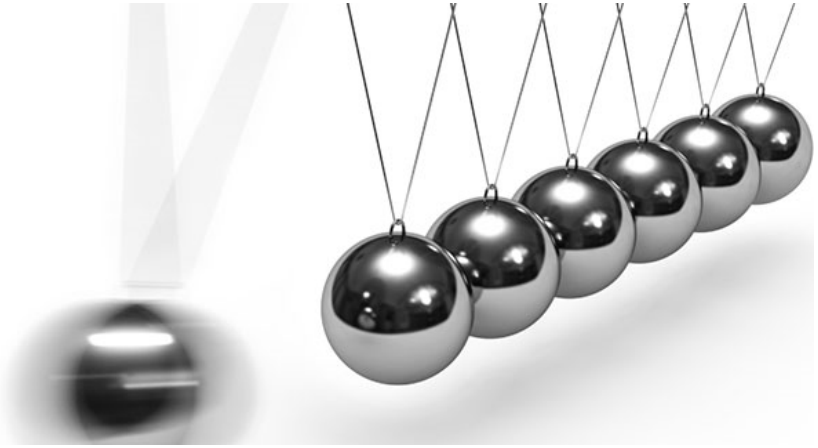
Infections

Disease transmission through organ transplantation

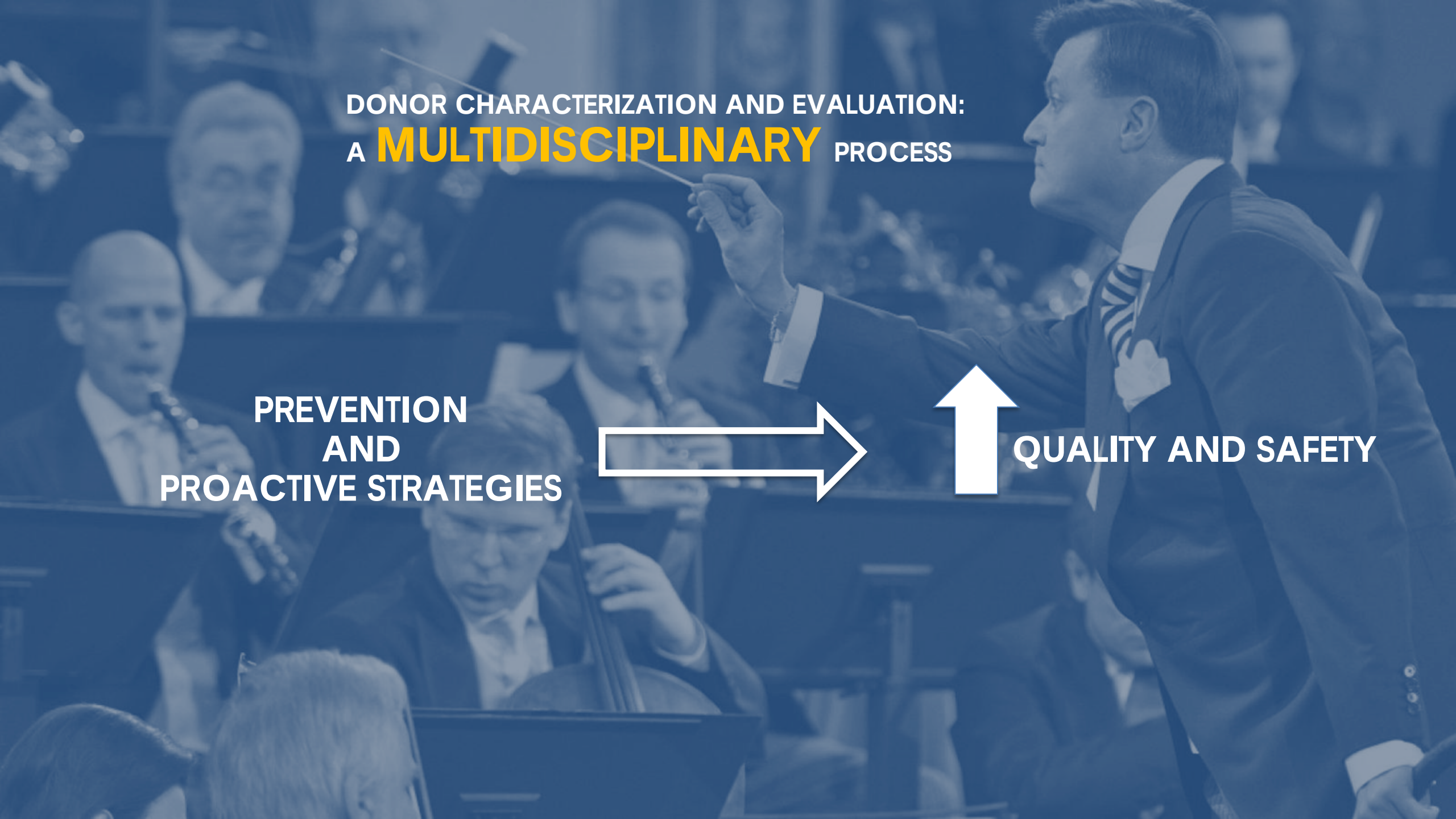
Impact

- Recipient — Survival and Quality of life
- Transplant / Medical team — Second victims
- Transplant / Health system — Credibility, trust, safety

Learning opportunity



Transmission: GETTING THE RIGHT BALANCE


DONOR CHARACTERIZATION AND EVALUATION:
A MULTIDISCIPLINARY PROCESS
PREVENTION
AND
PROACTIVE STRATEGIES
QUALITY AND SAFETY

Consensus Document on the Selection Criteria of Donors of Solid Organs in relation to Infectious Diseases . First Edition 2004

2004-2019

Recommendations for HTLV screening in organ donors:

Screening indicated in:
a) donors from or who have lived in endemic areas of HTLV 1 infection;
b) donors who are children of mothers born or residing in endemic area;
c) Donors whose partners have resided in endemic areas.

In this period **3 cases of organ donors with HTLV-I transmission** to patients transplanted

PAPER

Post-transplantation HTLV-1 myelopathy in three recipients from a single donor

J J Zarranz Imirizaldu, J C Gomez Esteban, I Rouco Axpe, T Perez Concha, F Velasco Juanes, I Allue Susaeta, J M Corral Carranceja

First case of HTLV-I transmission from organ donor in Spain

2003

Donor: young man born in Spain, Road accident. Donor after brain death.

Mother born in Venezuela. Retrospectively, it was found that, although she remained asymptomatic, she was seropositive for HTLV-I.

Once the first case was detected, a serological determination for HTLV-I (ELISA and western blot) was performed on stored blood from the donor. Those determinations resulted positive.

The **liver, both kidneys, the heart, and both corneas** were used for transplantation.
Liver and kidney recipients: myelopathy and paraplegia (18-24 months postx).

Heart transplantation, no information reported.
Patients who received the **cornea: HTLV-I negative**.

Second case of HTLV-I transmission from organ donor in Spain

2005

Donor: Woman born in Bolivia. Donor after uncontrolled circulatory death.

Bolivia was not in the list of countries with HTLV test at that moment.

Only one kidney was transplanted, patient developed spastic paraparesis 24 months after transplant

Third case of HTLV-I transmission from organ donor in Spain

2015

Donor: 38 year old man, born in Spain. Donation after controlled circulatory death**.**

Corneas were also retrieved – HTLV screening at tissue bank 24 h after organs procurement (positive).

Epidemiological risk factors: Sexual partner from endemic country (non detected during the organ donation process).

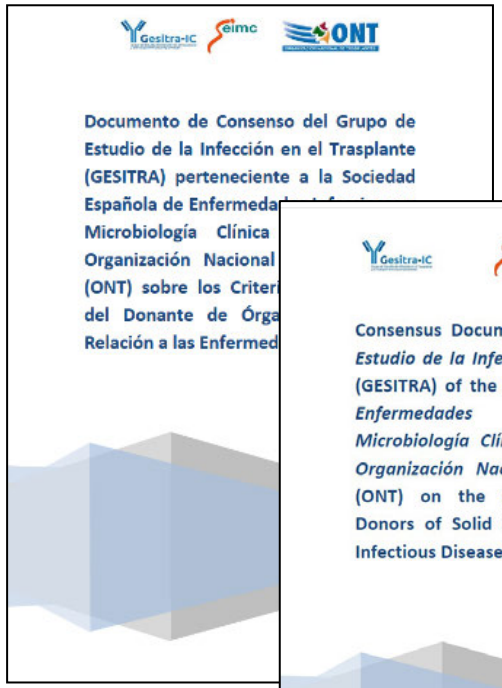
Both kidneys transplanted

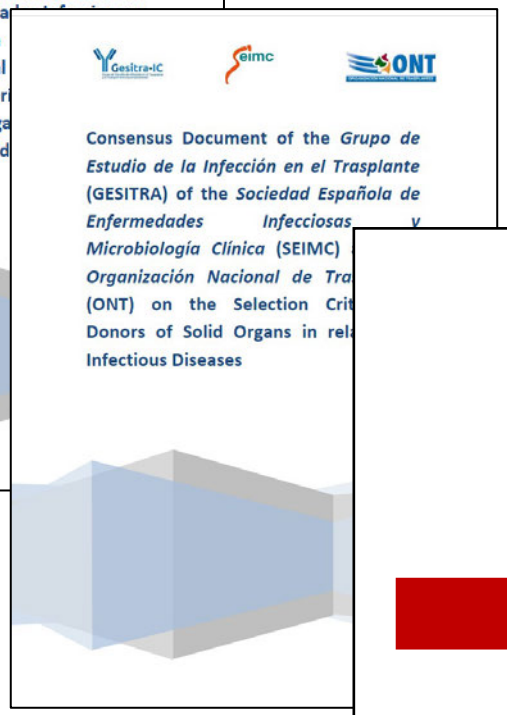
- First patient: TSP/HAM within 1 year in one recipient, despite antiretroviral prophylaxis attempted within the first weeks.

- Second patient: seroconverted for HTLV-1 but the kidney had to be removed soon due to rejection. Immunosuppression was stopped and the patient remains in dialysis but otherwise asymptomatic.

Considering…

- Global spread of HTLV
- Asymptomatic carriers
- No vaccine or antivirals
- Limitations of donor history (medical, social and behavioural data), donor history from relatives. short period of time to evaluate deceased donors.
- Poor prognosis in patients transplanted (Immunosupression)
- Available tests for screening (Enzime immunoassay .EIA-, indirect imunofluorencence –IIF-, others, Western blot for confirmatory tests)





13. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED HUMAN T-LYMPHOTROPIC VIRUS 1 (HTLV-1) INFECTION?

A. Transmission risk: RL1.

B. Recommendations

- Universal screening with serology in all donors through automated, approved tests that are efficient, fast with an adequate cost. AII.
- Screening is especially indicated in: a) donors from or who have lived in endemic areas of HTLV-1 infection; b) donors who are children of mothers born or residing in endemic area; c) donors, especially women, whose partners have resided in endemic areas. BII.
- In the case of seropositive donor and seronegative recipient, reject the organ. AII.
- In the case of seropositive donor and seropositive recipient for HTLV-1, assess acceptance of the organ, by considering potential lower risks of associated disease development in already infected subjects. BII.

GOBIERNO DE ESPAÑA MINISTERIO DE SANIDAD

ONT ORGANIZACIÓN NACIONAL DE TRASPLANTES

13. WHAT COURSE OF ACTION SHOULD BE UNDERTAKEN IN CASES OF SUSPECTED HUMAN T-LYMPHOTROPIC VIRUS 1 (HTLV-1) INFECTION?

A. Transmission risk: RL1.

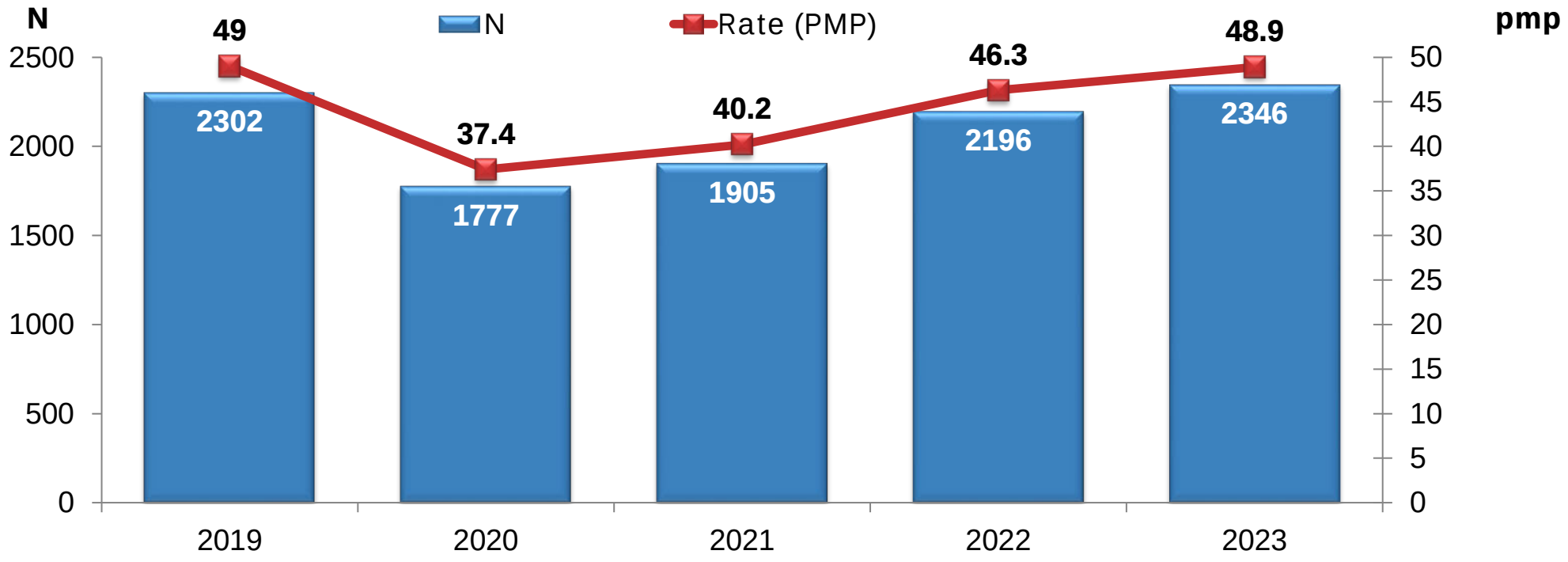
B. Recommendations

- Universal screening with serology in all donors through automated, approved tests that are efficient, fast with an adequate cost. AII.

- **National Transplant Committee approval**
  17 Regions (competent authorities)
  185 hospital authorized for organ procurement
  45 hospitals authorized for organ tx

- **Period (6 months) to implement the HTLV test in hospitals**

Number of false positive tests???



	2019 (July)	2020	2021	2022	2023
HTLV I-II +	**3** (1/1000)	**1** (0.6/1000)	**8** (4/1000)	**3** (1/1000)	**6** (2.5/1000)

Number of potential organ donors contraindicated due to HTLV I-II

Conclusion

Thank you!

AGENȚIA NAȚIONALĂ de TRANSPLANT

EXPERIENCE OF HTLV-1 IN ROMANIA AND THE STRATEGIES FOR TESTING DONORS FOR HTLV-1.

Dr. Guenady Roumenov Vatachki

Executive Director

National Transplant Agency

Stockholm at the ECDC SoHO-Net Organs meeting.

The threat of viral disease in transplantation

- Opportunistic infections cause considerable morbidity and mortality in transplant recipients
- Common viral threats
  - CMV
  - HHV-6, HHV-7, HSV-1, HSV-2, EBV, and VZV
  - These viruses may have direct or indirect effects, or may interact with each other or other viruses
- Emerging viral threats
  - SARS and West Nile Virus
  - Community acquired respiratory viruses
    - Respiratory Syncytial Virus (RSV), Influenza virus, Avian influenza (H5N1),
    - Rhinovirus, Enterovirus, Adenovirus, Coronavirus,

Legislation – mandatory testing

HIV 1 şi 2	antibodies anti-HIV-1,2	
Hepatita B	antigen Hbs	
	antibodies Anti HBc	
Hepatita C	antibodies anti-HCV	

Legislation

- HTLV-I antibody testing should be performed in the case of donors who live or come from areas with high prevalence or who have sexual partners from those areas or when the parents of the donors come from those areas.
- Additional testing may be required in certain circumstances, depending on the donor's travel and the characteristics of the donated organ, tissues or cells (eg: malaria, CMV, T. cruzi)
- For donations, blood samples must be obtained at the time of each donation.

Prevalence

- In Romania, the HTLV-1 prevalence has been reported to be 5.3/10,000 among first-time blood donors, and 3-25% in poly-transfused patients.
- In non-endemic areas, due to the migration of people and the sexual transmission of the virus, HTLV-1 and 2 have also been detected.

In practice- solid organs donor testing Hystocompatibility

- HLA A low-resolution
- HLA B low-resolution
- HLA C low-resolution
- HLA DRB1 low-resolution
- HLA DQA1 low-resolution
- HLA DQB1 low-resolution
- HLA DPA1 low-resolution
- HLA DPB1 low-resolution

Immunological risk assessment:
Crossmatch Luminex

In practice- solid organ donor testing viral screening

- AgHBs
- AgHBe
- Anti-HBe
- Anti-HBc
- Anti-HBs
- Anti-HCV
- CMV IgG
- CMV IgM
- EBV IgG
- EBV IgM
- HAV IgG
- HAV IgM
- HIV
- HTLV 1/2
- Syphilis
- Toxoplasma IgG
- Toxoplasma IgM
- Screening SARS-CoV-2 RT-PCR (GeneXpert)

In practice- solid organ donor testing tumoral screening

- AFP
- CEA
- CA 19-9
- CA 125
- CA 15-3
- PSA Total
- PSA Free

Renal recipient testing histocompatibility/ ambiguity solving

- HLA A low-resolution
- HLA B low-resolution
- HLA C low-resolution
- HLA DRB1 low-resolution
- HLA DQA1 low-resolution
- HLA DQB1 low-resolution
- HLA DPA1 low-resolution
- HLA DPB1 low-resolution

- HLA A high-resolution
- HLA B high-resolution
- HLA C high-resolution
- HLA DRB1 high-resolution
- HLA DQA1 high-resolution
- HLA DQB1 high-resolution
- HLA DPA1 high-resolution
- HLA DPB1 high-resolution

Renal recipient testing
Immunological risk assessment

- Anticorpi anti HLA clasa I si clasa II
- Single antigen clasa I (identificare clasa 1)
- Single antigen clasa II (identificare clasa 2)
- C1q clasa I
- C1q clasa II
- Crossmatch Luminex
- Autocrossmatch

Renal recipient testing viral screening

- AgHBs
- AgHBe
- Anti-HBe
- Anti-HBc
- Anti-HBs
- Anti-HCV
- CMV IgG
- CMV IgM
- EBV IgG
- EBV IgM
- HAV IgG
- HAV IgM
- HIV
- HTLV 1/2
- Sifilis
- Toxoplasma IgG
- Toxoplasma IgM
- Screening SARS-CoV-2 prin RT-PCR (GeneXpert)

Renal recipient testing tumoral screening

- AFP
- CEA
- CA 19-9
- CA 125
- CA 15-3
- PSA Total
- PSA Free

Post transplant testing renal transplant

- Antibodies anti HLA clasa I si clasa II
- Single antigen clasa I (identification clasa 1)
- Single antigen clasa II (identification clasa 2)
- ADN CMV - Real Time PCR
- ADN EBV - Real Time PCR
- ADN VHB - Real Time PCR
- ARN HDV - Real Time PCR
- ARN VHC - Real Time PCR
- ADN BKV - Real Time PCR
- ADN Parvovirus B19 - Real Time PCR
- *** if receptors cu AgHBs present- ADN VHB - Real Time PCR
- *** If receptors HCV present ARN VHC - Real Time PCR

Monitoring the immunosuppression post renal transplant

- Ciclosporina C0 si C2
- Tacrolimus
- Sirolimus

Tumoral Screening

- AFP
- CEA
- CA 19-9
- CA 125
- CA 15-3
- PSA Total
- PSA Free

Summary

- Viral infections cause considerable morbidity and mortality in transplant recipients
- Viral threats exist
  - HHV-6, HHV-7, HSV, VZV, EBV, polyomaviruses, RSV, influenza, WNV
- viral threat still the most significant pathogen in SOT recipients
  - Direct and indirect effects
  - Subclinical viral replication
  - Interaction with other viruses
- HTLV testing is common in SOT in Romania because we are endemic area.

Conclusions

policies regarding HTLV

- all Blood donor screening ;
- Preventing the mother-to-child transmission of HTLV-1 by screening pregnant women from endemic areas,
- all SOD screening
- for assisted reproduction technologies HTLV-I antibody testing should be performed in the case of donors who live or come from areas with high prevalence or with sexual partners from those areas or when the parents of the donors come from those areas
- There are no other HTLV-1-related health policies in Romania
- No consistent screening for children born from positive mothers.

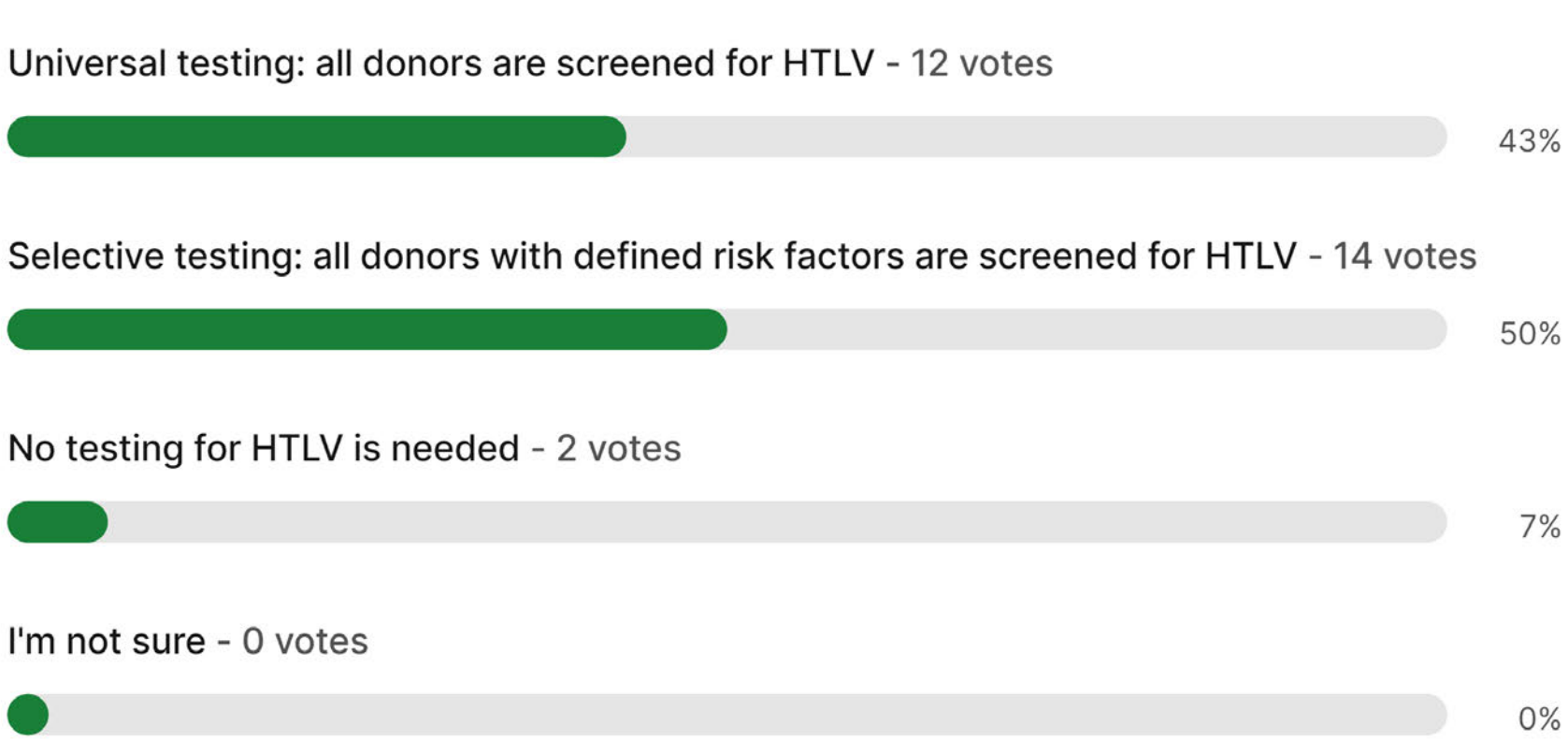
THANKS

FOR YOUR ATTENTION

And to finish...

Considering the discussions in this session, what do you think screening strategy for HTLV in deceased organ donation in your country should be?

Multiple Choice Poll 28 votes 28 participants



Session 6
Conclusion of day 1
18 June

Session 7
Biovigilance and reporting of serious adverse reactions and events
19 June

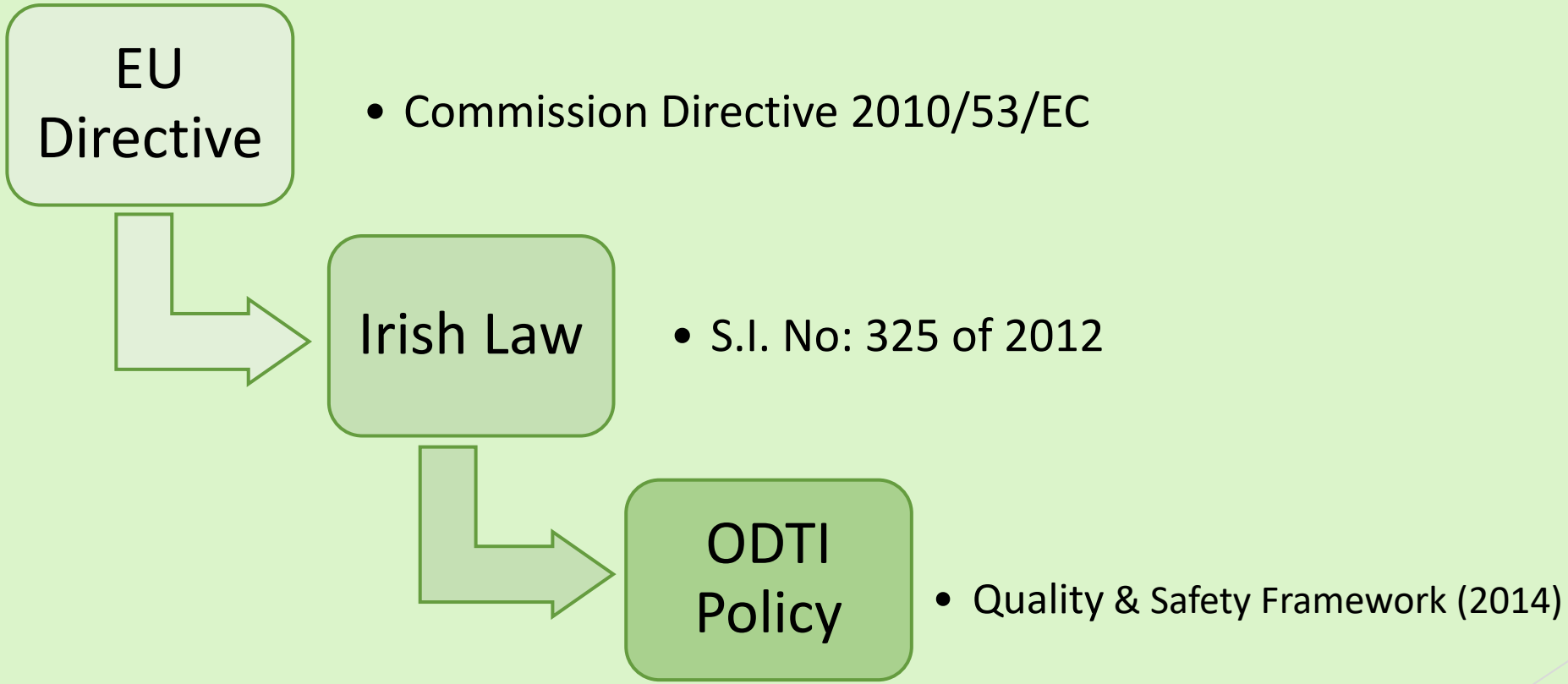
Session overview

1. **Issues in reporting serious adverse reactions and events for Organs** – Paul Hendrick, Organ Donation Transplant Ireland, HSE, Ireland
2. **Biovigilance guideline repository** – Francois-Xavier Lamy, ECDC
3. **SARE reporting – communicable diseases transmission cases** – Ana Paula Barreiros, NFP, Germany
4. **Discussion** – All
5. ***Strongyloides stercoralis* transmission through organs – case report** – Sophie Lucas Samuel, NFP, France and Morten Hagness, Oslo University Hospital, Norway
6. **Questions and answers** – All

Biovigilance Implementation The Irish Experience

Paul Hendrick,
Director of Quality ODTI

Regulatory Landscape



Regulatory Landscape
National Competent Authority - Joint

Delegated from the SI by the Department of Health

- Non Clinical – Health Products Regulatory Authority (HPRA) (Regulator for Medical Devices, Medicines, Blood and Tissue – including vigilance on all)

- **Clinical – Organ Donation Transplant Ireland**

Operational Landscape – Transplantation in Ireland

Pre Procurement

- 6 CLOD Regional
- 6 ODNM Regional
- Covering 26 x ICU
- Regulatory Gap

Procurement

- NOPS
- Centralised
- 10 Donor Coordinators
- Licensed to SI / EU Directive

Transplantation

- Heart / Lung Tx Centre
- Liver / Pancreas Tx Centre
- Kidney Tx Centre
- Licensed to SI / EU Directive

Organisation Development

Year	Milestone Event	Biovigilance System in Place
2012	Established ODTI - Clinic Lead Appointed / Function Established in Health System with clerical support / NODTAG	Manual SARE Reports reviewed with relevant NODTAG– all manual
2012 - 2014	Establish & Licensed Transplant Centre QMS – mandated SARE reporting	
2014	Quality & Safety Framework Policy Developed and Adapted	
2015	Establish & Licensed NOPS QMS - SARE reporting	Manual SARE Reports reviewed with relevant NODTAG– all manual – basic Excel Sheet with basic reports / email communication etc.
2015 - 2022	Development of NOPS / Transplant QMS & Services / Covid	
2022 – To Date	Established dedicated ODTI Quality Biovigilance Function	Biovigilance Road Map Next

Reporting to Date

- 169 Reports (2012 – now – 07 June 2024 latest report)
- 163 Clinical (>96%) / 6 Non Clinical
- SAE – 147 / SAR – 20 / Incorrect reports 2
- Reporting level is satisfactory
- Reporting of Issues which are technically outside the definition

Bio Vigilance Roadmap

Process

- Biovigilance Process (aligned to EDQM – Quality & Safety)
- Associated Continuous Improvement Process

Organisation

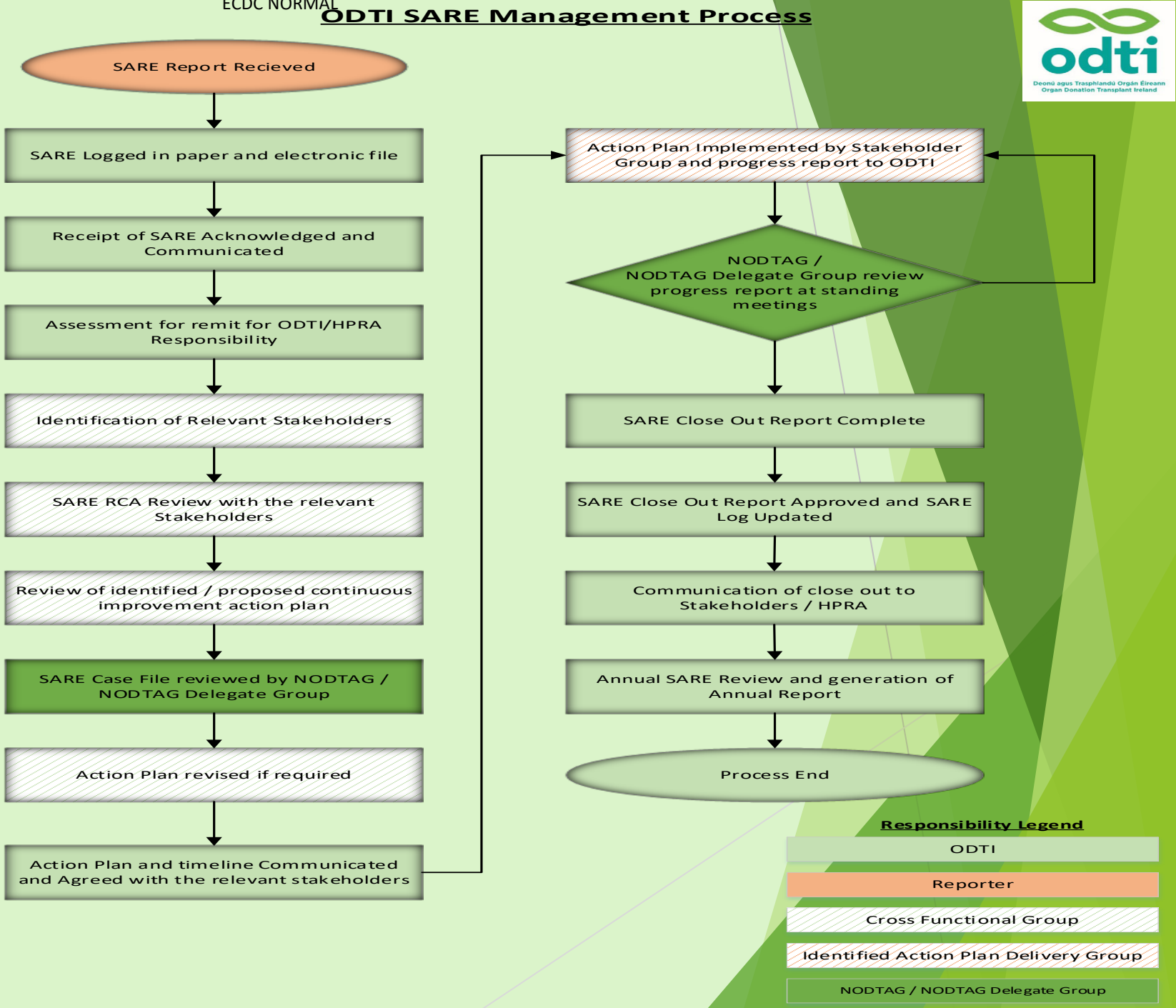
- ODTI person with responsibility for Biovigilance
- Clinical Governance – Independent Sub Committee
- Continuous Improvement Implementation Group
- ODTI membership on VES Group / Liaison with NCA

Systems

- Electronic Reporting System & Database
- Rapid Alert utilising NOPS Donor System

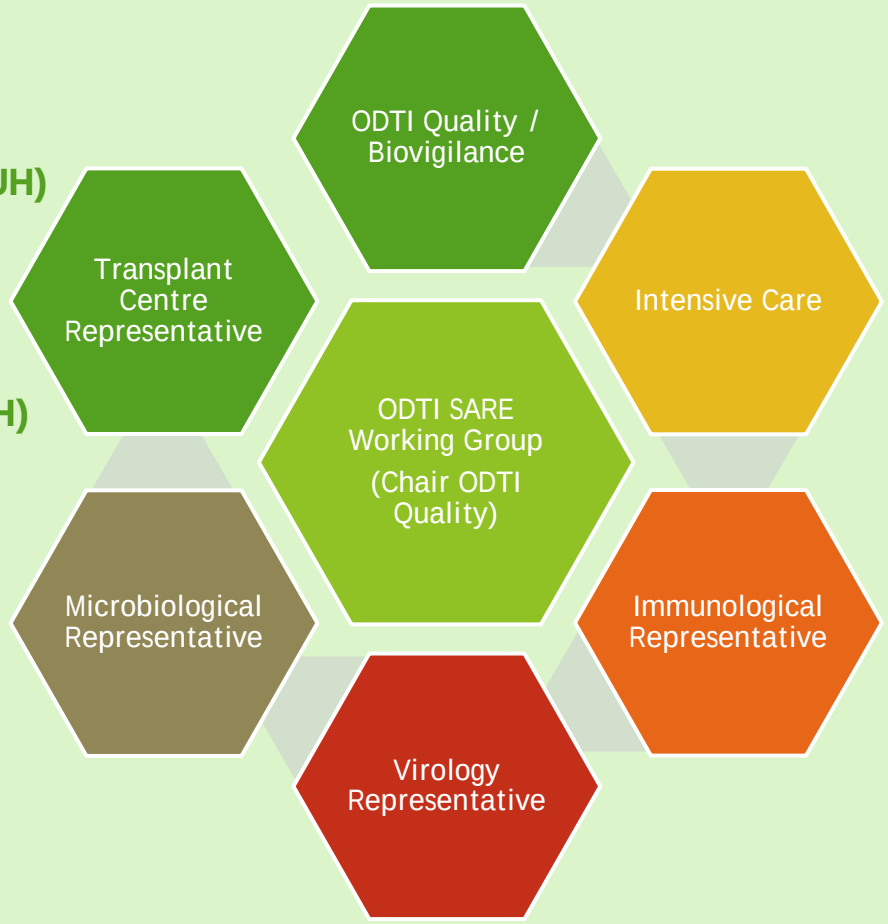
Agreed SARE Process

- Reviewed and Agreed with HPRA – Joint Competent Authority
- Endorsed and Agreed with NODTAG
- Process Proceduralised within ODTI



SAR/E Working Group

Claire Dalton



Dr. Michelle Murray (MMUH)

Mr. Ian Robertson (BMT)

Dr. Audrey Dillion (SVUH)

Dr. Catherine Motherway

Dr. Sinead McDermott

Prof. Mary Keoghan

Dr. Daniel Hare

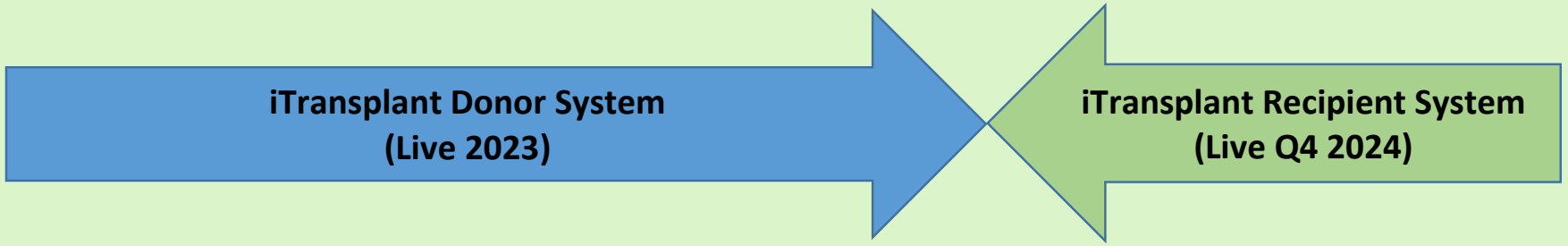
SARE Working Group

- To provide the clinical oversight and direction for the :
  - Review Report Classification
  - Review of investigation report
  - Management of the SARE
  - Continuous improvement actions
  - Recommendations for further corrective actions / learning
  - Contribute BV Section to ODTI Annual Report

SARE Working Group

- To provide the clinical oversight and support for ODTI participation in VES and others/relevant groups:
  - Report Review for Irish Annual Submission *on behalf of ODTI or in conjunction with HPRA
  - Review of European wide report(s)/working groups to identify continuous improvement initiatives for Ireland

Operational Landscape
Electronic Systems Introduction



Biovigilance Systems Challenge # 1
Rapid Alert Notification / Tracking

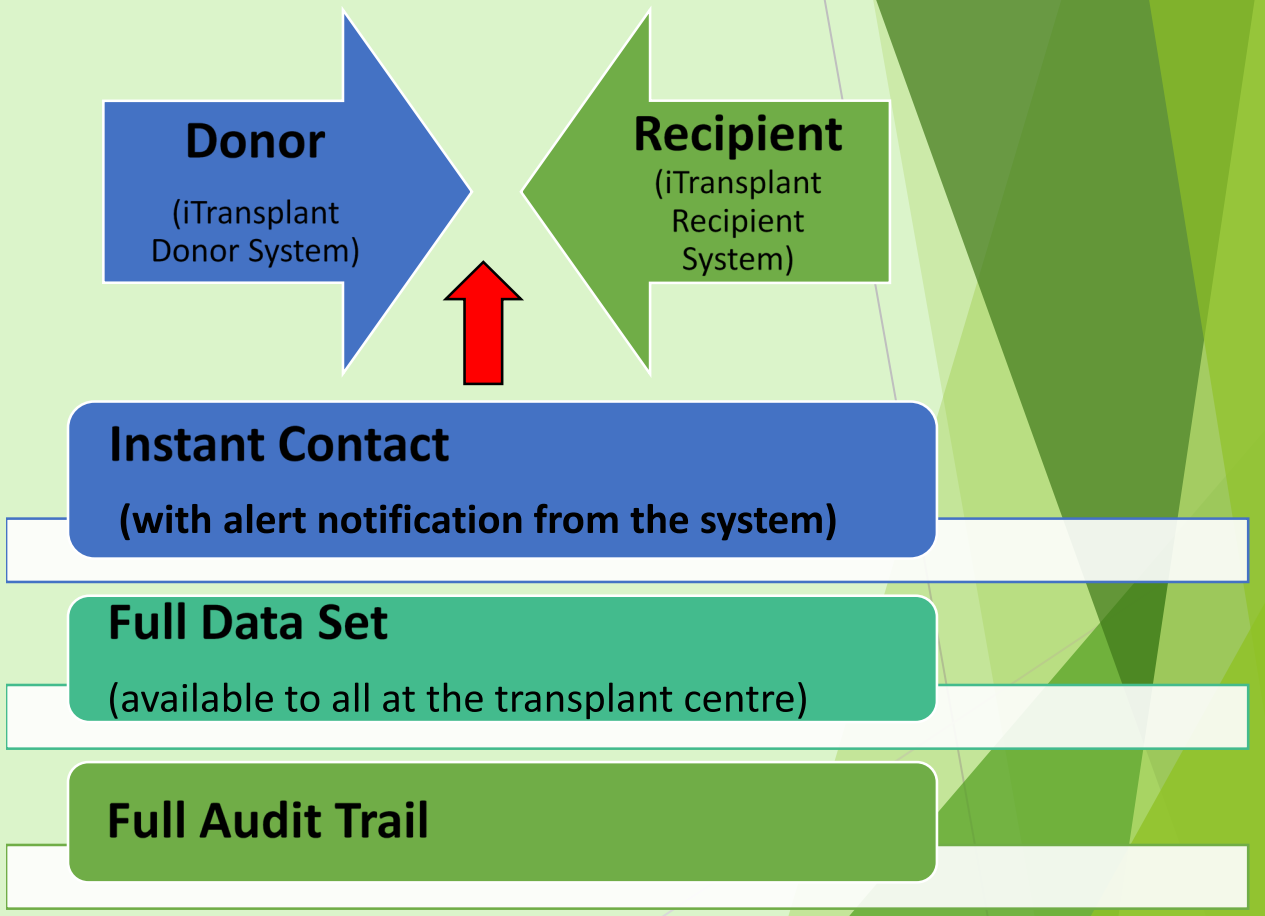
- Predominantly Retrospective Information
- No Quarantine
- No Recall
- Normally Transplanted
- Immediate Patient Action Required by the Transplant Physicians
- Current Process Phone Call / Email from Procurement Service

Continuous Improvement Initiative

Rapid Alert Notification

- Trigger Retrospective Information Event on Procurement Service – Donor System (EOS)

- Automatic simultaneous update to all relevant Transplant Centres immediate attention (on Recipient System)
  - eMail
  - Text
  - Call



Biovigilance Systems Challenge # 2 Reporting System

- Paper Form – Scanned and eMail
- Basic Excel Log
- No Case Management System

Continuous Improvement Initiative # 2

Case Reporting

- Accessible
- User Friendly

Case Management

- Report Management
- Investigation Management
- Communication
- Root Cause Analysis
- Risk Determination

Continuous Improvement Plan

- Define
- Measure
- Analyse
- Improve
- Control

Continuous Improvement Initiative # 2

Case Reporting

- Accessible
- User Friendly

Case Management

- Report Management
- Investigation Management
- Communication
- Root Cause Analysis
- Risk Determination

Continuous Improvement Plan

- Define
- Measure
- Analyse
- Improve
- Control

Developed Reporting System

- Immediate – Easier Pro-forma on Websites & dedicated Biovigilance eMail Address
- Extension to iTransplant (Donor / Recipient System) or
- Follow B&T with Dendrite System

Developed Case Management System

- Immediate – expansion of excel functionality act as Database for all activity
- Utilise CAPA functionality of Q-Pulse – electronic Quality Management System, or
- Expand iTransplant / Dendrite functionality to accomodate

Thank You

Questions ?

SARE reporting – communicable diseases transmission cases

Ass. Prof. Ana Paula Barreiros, MD

Deutsche Stiftung Organtransplantation (DSO), OPO Germany

Stockholm/Sweden, 19.06.2024

DEUTSCHE STIFTUNG ORGANTRANSPLANTATION
Gemeinnützige Stiftung

Koordinierungsstelle Organspende

Reporting of SAE / SAR in Germany

Agenda

1. **Definition of SAE /SAR and legal principles of SAE / SAR reporting**
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Reporting of SAE / SAR in Germany

EU Directives 2010/53/EU and 2012/25/EU

2010/53/EU

DIRECTIVE 2010/53/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 7 July 2010

on standards of quality and safety of human organs intended for transplantation

Article 11

Reporting system and management concerning serious adverse events and reactions

1. Member States shall ensure that there is a reporting system in place to report, investigate, register and transmit relevant and necessary information concerning serious adverse events that may influence the quality and safety of organs and that may be attributed to the testing, characterisation, procurement, preservation and transport of organs, as well as any serious adverse reaction observed during or after transplantation which may be connected to those activities.

2012/25/EU

DIRECTIVES

COMMISSION IMPLEMENTING DIRECTIVE 2012/25/EU

of 9 October 2012

laying down information procedures for the exchange, between Member States, of human organs intended for transplantation

(Text with EEA relevance)

Article 7

Reporting of serious adverse events and reactions

Member States shall ensure that the following procedure is implemented by their competent authorities or delegated bodies:

(a) Whenever the competent authority or delegated body of the Member State of destination is notified of a serious adverse event or reaction that it suspects to relate to an organ that was received from another Member State, it shall immediately inform the competent authority or delegated body of the Member State of origin and transmit without undue delay to that competent authority or delegated body an initial report containing the information set out in Annex I, in so far as this information is available.

Reporting of SAE / SAR in Germany

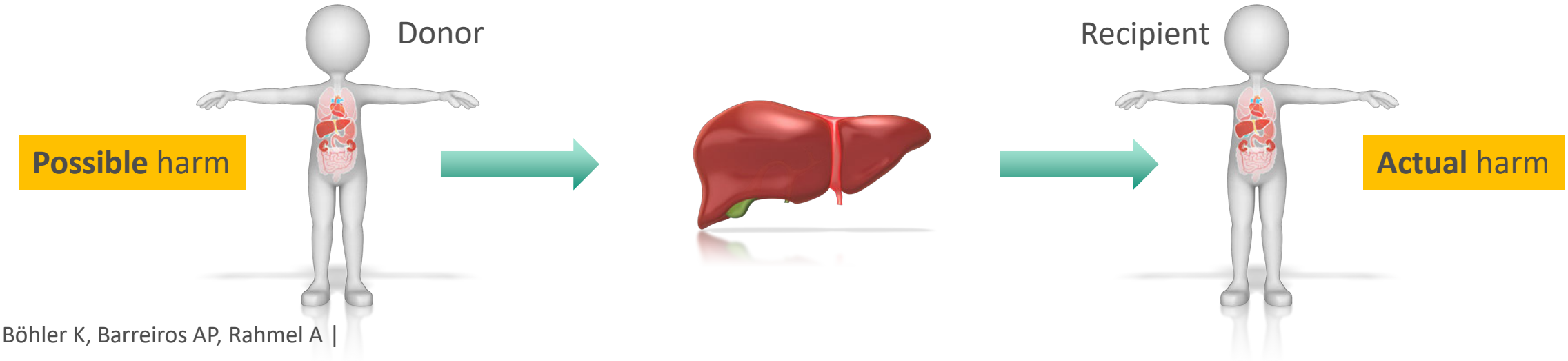
Definition of SAE and SAR according to EU Directive 2010/53/EU/Efretos project

Serious Adverse Event (SAE)

„… any undesired and unexpected occurrence associated with any stage of the chain from donation to transplantation that might lead to the transmission of communicable disease, to death or life-threatening, disabling or incapacitating conditions."

SAR = serious adverse reaction (SAR)

„ … an unintended response, including a communicable disease, … in the recipient that might be associated with any stage of the chain from donation to transplantation that is fatal, life-threatening, disabling, incapacitating, or which results in, or prolongs, hospitalization or morbidity."



Reporting of SAE / SAR in Germany

Legal foundation: German Transplantation Law (TPG)

§ 11 Zusammenarbeit bei der Entnahme von Organen und Geweben, Koordinierungsstelle

…

(1a) Die Koordinierungsstelle hat die Zusammenarbeit zur Organentnahme bei verstorbenen Spendern und die Durchführung aller bis zur Übertragung erforderlichen Maßnahmen mit Ausnahme der Vermittlung von Organen durch die Vermittlungsstelle nach § 12 unter Beachtung der Richtlinien nach § 16 zu organisieren.

…

Hierzu erstellt die Koordinierungsstelle geeignete Verfahrensanweisungen unter Beachtung der Richtlinien nach §16, insbesondere

…

9. zur Sicherstellung der unverzüglichen Meldung schwerwiegender Zwischenfälle und schwerwiegender unerwünschter Reaktionen und der in diesem Zusammenhang getroffenen Maßnahmen auf der Grundlage der Rechtsverordnung nach § 13 Absatz 4.

Important:
The German organ procurement organisation (DSO) is the delegated body assigned by the national authority (Federal ministry of health)

Responsible for tisssue donation – Paul-Ehrlich-Institut (PEI)
Responsible for living donation – Transplantation center

Reporting of SAE / SAR in Germany

Procedural Instructions and Notification Form

VII.

B. BESONDERER TEIL

Verfahrensanweisung zur Sicherstellung der unverzüglichen Meldung SCHWERWIEGENDER ZWISCHENFÄLLE (SAE) und SCHWERWIEGENDER UNERWÜNSCHTER REAKTIONEN (SAR) und der in diesem Zusammenhang getroffenen Maßnahmen auf der Grundlage der Rechtsverordnung nach § 13 Abs. 4 TPG (§ 11 Abs. 1a Nr. 9 TPG)

Grundsätze

In den Verfahrensanweisungen ist unter IV. die Befundübermittlung geregelt, welche durch die Verfahrensanweisung VI. zur Rückverfolgbarkeit komplementiert wird. Für die Meldung schwerwiegender Zwischenfälle und schwerwiegender unerwünschter Reaktionen gelten die nachfolgenden Regelungen. Im Folgenden wird für den Begriff „schwerwiegender Zwischenfall" die Abkürzung für den englischen Fachbegriff „Serious Adverse Event" (SAE) und für den Begriff „schwerwiegende unerwünschte Reaktion" die Abkürzung für den englischen Fachbegriff „Serious Adverse Reaction" (SAR) verwendet.

Meldung SAE/SAR an Koordinierungsstelle

Empfänger

Tel.: 0800 376 7273
Per Telefax an: +49 (69) 677 328-89998
Deutsche Stiftung Organtransplantation
SAE/SAR-Meldung
Deutschherrnufer 52 | 60594 Frankfurt am Main

Absender bitte vollständig ausfüllen

_____

_____

_____

Telefon: _____

Telefax: _____

Ansprechpartner: _____

Meldung schwerwiegender Zwischenfälle (SAE) und/oder einer schwerwiegenden unerwünschten Reaktion (SAR) gemäß § 9 Abs. 2 und § 10 Abs. 4 TPG Organ V sowie § 40 Abs. 3 AMWHV

Art der meldenden Einrichtung

- ☐ TXB des Entnahmekrankenhauses
- ☐ Behörde
- ☐ Transplantationszentrum
- ☐ Gewebeeinrichtung
- ☐ sonstige _____
- ☐ Arzt der Leichenschau
- ☐ von der DSO beauftragte Dritte (z.B. Labor)
- ☐ Eurotransplant

Fallidentifikationsnummer des Entnahmekrankenhauses:

_____

bei Geweben Identifikations-Nr.: _____

DSO-Kennnummer, falls bekannt: _____

ET-Spendernummer/ET-Empfängernummer, falls bekannt: _____

Transplantationsdatum, falls bekannt: _____

Entnahmedatum, falls bekannt: _____

gemeldet am: _____

Gesprächspartner: _____

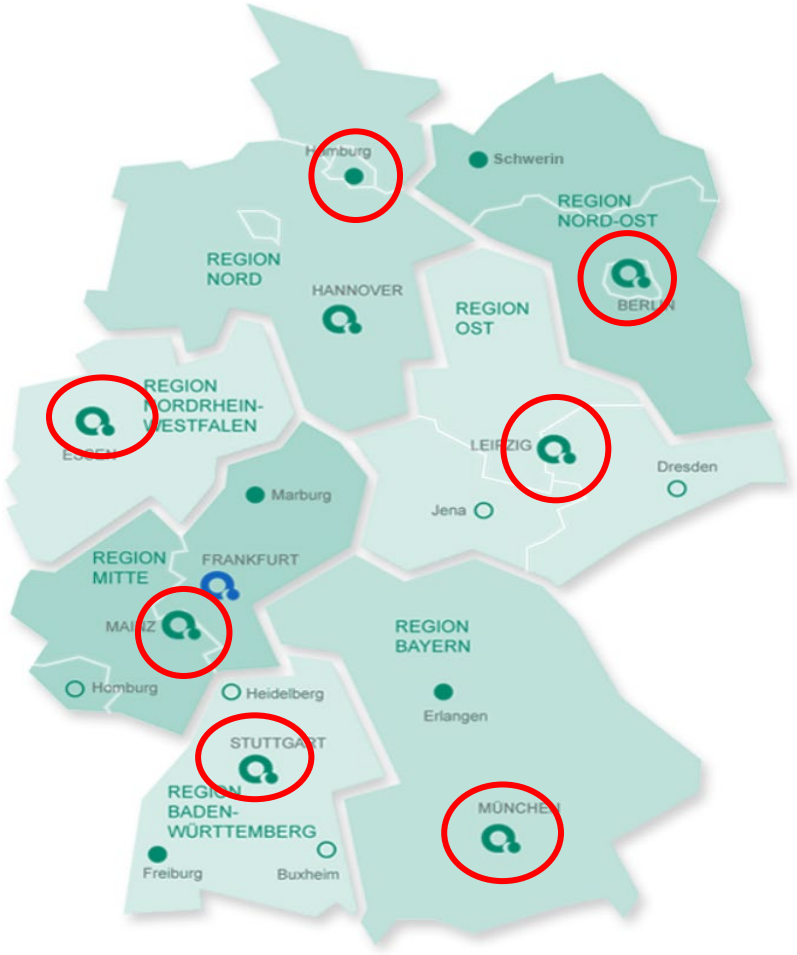
Meldungsdetails

Bitte beschreiben Sie hier den schwerwiegenden Zwischenfall und/oder die schwerwiegende unerwünschte Reaktion so genau wie möglich unter Meldung aller sachdienlichen und notwendigen Angaben. **Sollte der Platz nicht ausreichen, fügen Sie ein weiteres Blatt hinzu.**

Bitte fügen Sie auch sämtliche Befunde diesem Telefax bei!

Reporting of SAE / SAR in Germany

7 regions, each with 1-2 medical colleagues working in the SAE / SAR team 24/7



Reporting of SAE / SAR in Germany

Team and Contact SAE / SAR 2024

Ressortleitung **PD Dr. Ana Paula Barreiros**
Stabsstelle SAE/SAR **Dr. Klaus Böhler**
Regionale Koordinatoren
Karsten Tiede (Nord)
Dr. Thorsten Doede (Nord-Ost)
Dr. Monika Scholle (Ost)
N.N.(NRW)
Sören Melsa, Ruth Lindner (Mitte)
Dr. Carl-Ludwig Fischer-Fröhlich,
Kevin Otero (Ba-Wü)
Susanne Schmidt (Bayern)

SAE/SAR – Contact us
24/7

Telefon **0800 – 376 7273**
0800 – DSO SARE

Email **dso.sare@dso.de**

Fax 069 – 677 328 - 89998

Reporting of SAE / SAR in Germany

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Reporting of SAE / SAR in Germany

2023 Publication of six years German SAE / SAR data

Transpl Int. 2023 Sep 4:36:11610. doi: 10.3389/ti.2023.11610. eCollection 2023.

Vigilance Data in Organ Donation and Solid Organ Transplantation in Germany: Six Years of Experience 2016–2022

Klaus Böhler [1], Axel Rahmel [1], Ana Paula Barreiros [1]

Affiliations + expand

PMID: 37745644 PMCID: PMC10515207 DOI: 10.3389/ti.2023.11610

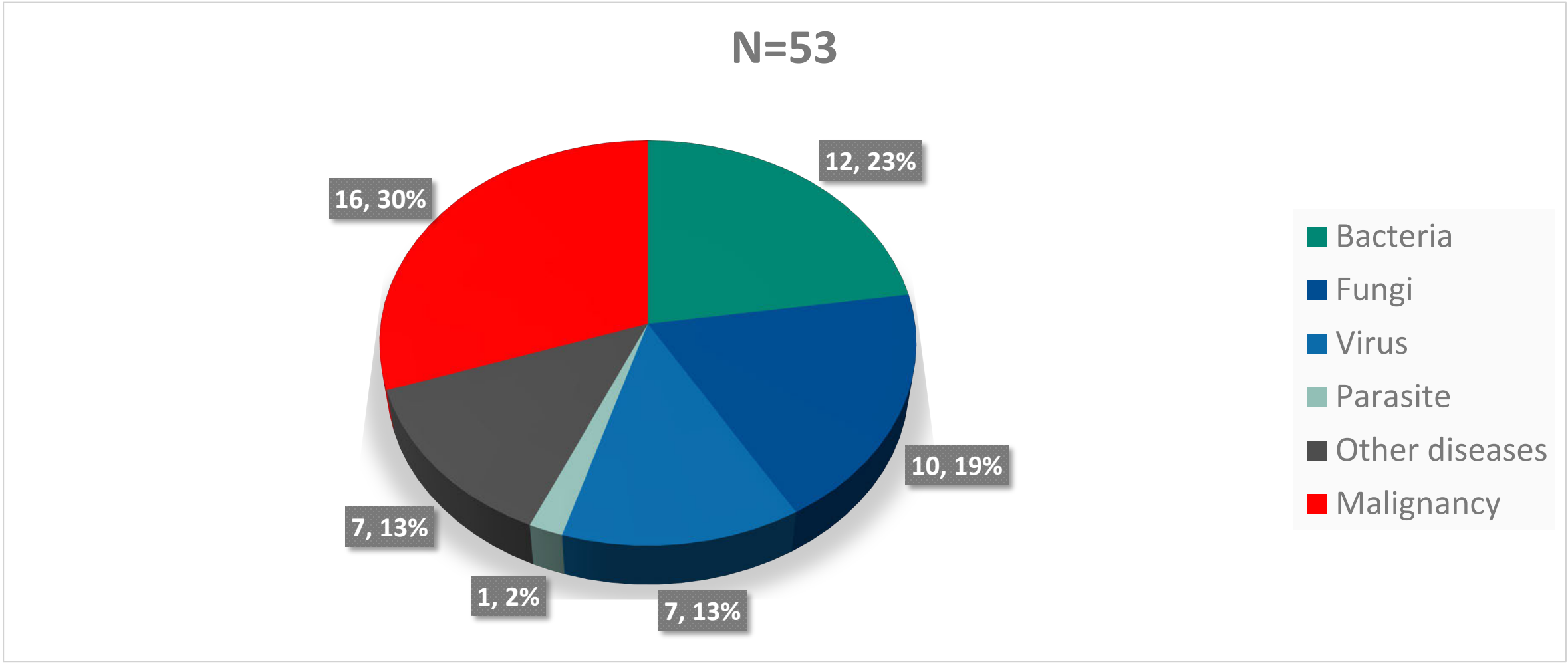
Free PMC article

Reporting of SAE / SAR in Germany

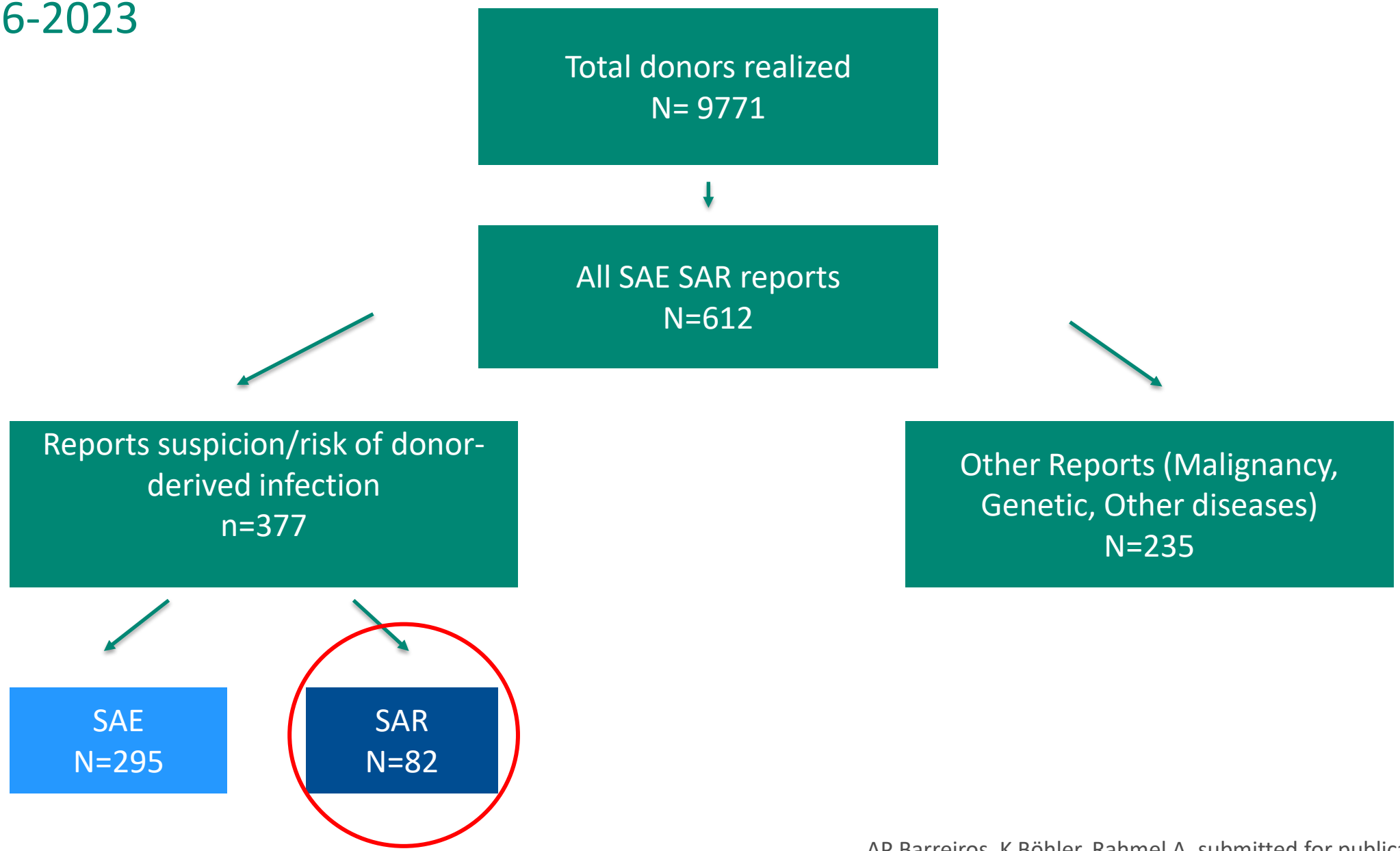
Six year German SAE / SAR data 2016-2022

- The reports from 01/2016 to 12/2022 were analysed by the SAE / SAR team of the DSO
- 21.060 organs were transplanted from 8.519 donors
- 543 SAE/ SAR reports have been received by the DSO
- 53 SAE / SAR report with probable / proven transmission of a disease from the donor to one (or more) recipients

Reporting 2016-22: Categorization of cases with p/p transmission



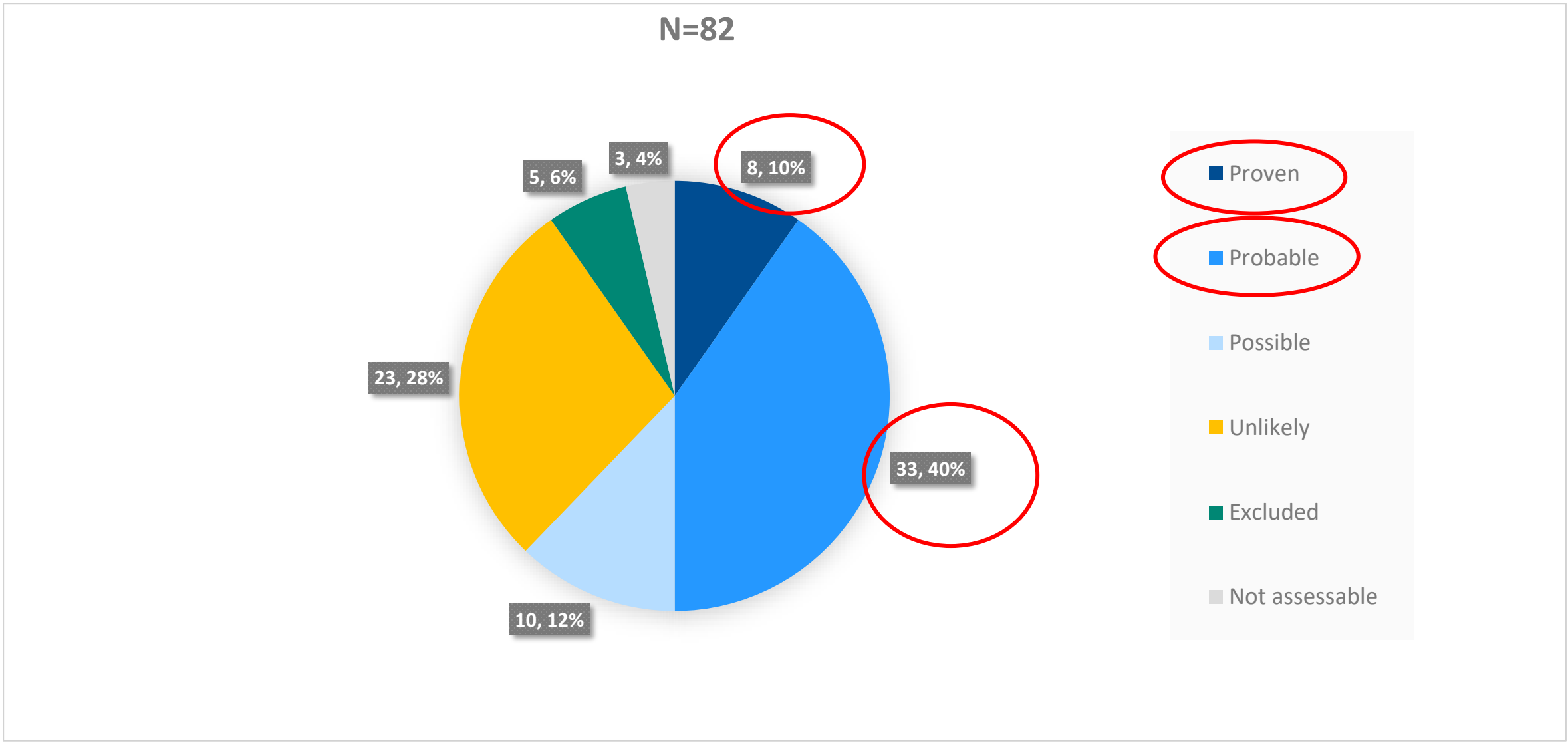
Reports with suspected Donor-derived infections (DDI) in Germany 2016-2023



AP Barreiros, K Böhler, Rahmel A, submitted for publication

SAR reports – imputability analysis

DDI in Germany 2016-2023



AP Barreiros, K Böhler, Rahmel A, submitted for publication

Categories of DDI in Germany 2016-2023

All pathogens – Type of pathogenes

	All Reports	P/P* donors	Recipients from P/P donors	Recipients with P/P transmission	Death from P/P Transmission
Bacteria	182	18	65	27 (42%)	0 (0 %)
Fungus	135	14	52	16 (31%)	3 (19%)
Virus	55	8	29	14 (48%)	3 (21%)
Parasites	5	1	4	1 (25%)	1 (100%)
Total	377	41	150	58 (39%)	7 (12%)

- P/P: proven/probable

Barreiros AP, Böhler K, Rahmel A, submitted for publication

Categories of DDI in Germany 2016-2023

Bacterial pathogens

	All Cases	MDR**	P/P donors	Recipients from P/P donors	Recipients with P/P transmission	Death from P/P Transmission
Staph. spp	64	20	1	3	1	0
Klebsiella spp	28	10	3	10	6	0
E.coli	25	5	4	11	5	0
Enterococcus	22	8	5	22	10	0
Pseudomonas	17	5	1	4	1	0
Mycobacteria	9	0	3	12	3	0
Other	102	27	1	3	1	0
Total	267*	75	18	65	27	0***

- * In 79 cases more than one pathogen ** MDR – multi drug resistant *** includes 6 organ loss (kidneys) , two due to Klebsiella , three due to Enterococcus and one due to Streptococcus.

Barreiros AP, Böhler K, Rahmel A, submitted for publication

Categories of DDI in Germany 2016-2023

Fungal pathogenes

	All Cases	P/P donors	Recipients from P/P donors	Recipients with P/P transmission	Graft loss	Death from P/P Transmission
Candida spp.	125	10	38	11 (29%)	6**	3
Aspergillus spp.	16	2	6	3 (50%)	0	0
Cryptococcus	2	2	8	2 (25%)	0	0
Other	5	0	0	0	0	0
Total	148*	14	52	16 (31%)	6	3 (19%)

- *In 13 cases more than one pathogen ** 4 kidneys and one kidney/pancreas, three of the recipients died
-

Barreiros AP, Böhler K, Rahmel A, submitted for publication

Categories of DDI in Germany 2016-2023

Viral pathogenes

	All Cases	P/P donors	Recipients from P/P donors	Recipients with P/P transmission	Death from P/P Transmission
HBV	9	1	3	1	0
HCV	7	1	5	5	0
HEV	5	2	6	2	0
BoDV-1	1	1	3	3	2
HHV-8	1	1	1	1	1
Other*	32	2	11	2	0
Total	55	8	29	14	3 (21%)

* Includes one CMV transmission (incorrectly reported CMV status of the donor) and one HHV -6 transmission to a child

Barreiros AP, Böhler K, Rahmel, submitted for publication

DDI in Germany 2016-2023: Cumulative Incidence

Total Donors recovered	**9771**
N(%) with risk/suspicious for DDI	295 (3,0%)
N(%) with Proven/Probable transmission	41 (0,42%)
Total recipients transplanted	**27919**
N(%) with Proven/Probable DDI transmission	58 (0,21%)
N(%) with deaths due to Proven/Probable transmission	7 (0,025%)

3 viral
3 fungal
1 parasite (Toxoplas.)

Barreiros AP, Böhler K, Rahmel A, submitted for publication

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Agenda

1. **Definition of SAE /SAR and legal principles of SAE / SAR reporting**
2. **Donor-Derived infections (DDI) in Germany 2016-2023**
3. **Results of the survey and pilot data collection EU Organ SAE/R reporting**
4. **Case report**
5. **Conclusion**

Case report

- **Kidney recipient in transplant center in the South of Germany (A):**
- Neurological symptoms 3.5 months post transplant
- Initially force reduction both legs, increasing until tetraplegia
- In addition progredient dysarthria, vigilance reduction, loss of cranial nerves reflexes, coma
- Nephrectomy 6 months post Tx (Histology: marginal interstitially nephritis, no hint for pathogens)
- Contact to transplant center of contralat. donor kidney (B): recipient passed away shortly before, with same symptoms and comparable course of disease
- **SAR-report 6.5 months pos Tx, information all involved transplant centers immediately**

Case report

- **Donor, 70 years, male**
- Origin: rural region in the south of Germany, married, two sons, decision pro donation lifetime
- Medical history: coronary heart disease, COPD, gout, thyreoidektomia, appendectomia
- Admission with abdominal pain unclear reason, no neurological symptoms
- Two days after admission resuscitation due to arrhythmia
- cCT: pansinusitis and signs for massive hypoxia: diagnosis of brain death
- **Organ procurement with**
- Transplantation of liver, both kidneys, no tissue

Case report

- Extensive analysis of clinical course and medical history, also social and familial history
- **No further information**

- Information: kidney recipient (A) passed away 7 months post Tx,
- No autopsy (denied by family)

Case report

- Biopsies of brains of both kidney recipients, also liquor and serum of kidney recipient A (Friedrich-Löffler-Institut, German Federal Institut for Veterinary medicine):

- Diagnostics for rabies plus Next-Generation-Sequencing NGS (metagenomdiagnostics, gensequenzing , search for foreign DNA/RNA)

- Detection of **Bornavirus-Genom (Mammalian 1 Bornavirus)** in high concentration in brain biopsy kidney recipient (A), confimation via realtime - PCR (Pan-Bornavirus-PCR).NGS: Genomsequencing of the whole genom. Minimaler detection in Liquor dieses of the patient. Detection Bornavirus-RNA in explanted kidney graft patienten (A) via realtime-PCR.

Case report

- Results confirmed via material of transplant center **B**: Pan-Bornavirus-PCR positiv.
- Parallel: immunhistological investigations on brain biopsies of patient B showed also Bornavirus-Antigen .
- First liquor samples, throat swap, urin and stool samples of the **liver recipient** initially Pan-Bornavirus-RT-PCR negativ, but then getting positive with developement of increasingly neurological symptoms (dysarthria, tremor, insecure walk)
- Exclusion of other transmission sources (ATG therapy e.g.)
- Cave: **Bornavirus was not known as human pathogenic !!**
  (only squirells, horses e.g.)

Publikation: New England Journal 10/2018

Fatal Encephalitic Borna Disease Virus 1 in Solid-Organ Transplant Recipients

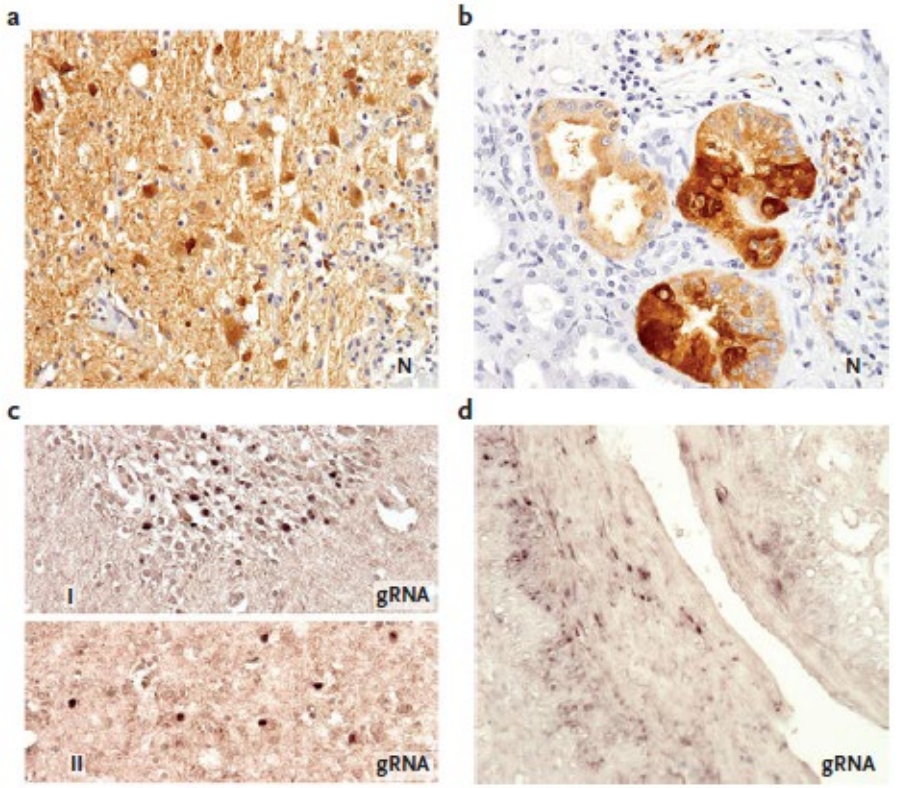
TO THE EDITOR: Borna disease virus 1 (BoDV-1; species *Mammalian 1 orthobornavirus*) causes progressive meningoencephalitis, mainly in horses and sheep. Evidence of BoDV-1 infection in humans is limited.[1,2] However, after the identification of a bornavirus transmitted by exotic pet squirrels — the variegated squirrel bornavirus 1 (species *Mammalian 2 orthobornavirus*)[3] — the zoonotic potential of mammalian bornaviruses should be considered. Here, we report evidence of donor-transmitted BoDV-1 infection occurring in three solid-organ transplant recipients, two of whom died.

Three organs (kidneys and liver) were obtained from a 70-year-old, white, male, brain-dead donor from the Bavarian region of southern Germany; the donor had no signs or symptoms of neurologic diseases or of an active infectious process. The kidneys were allocated to a 66-year-

and recipient 2 died on post-transplantation day 179. The liver graft was allocated to a 65-year-old man with hepatocellular carcinoma (recipient 3). On post-transplantation day 98, facial palsy, anomia, and cognitive deficits developed in the patient. Magnetic resonance imaging revealed a leukoencephalopathy (Fig. 1A). Recipient 3 is currently in remission from the disease and has optic nerve atrophy (Table S1 in the Supplementary Appendix, available with the full-text of this letter at NEJM.org). The findings from assessment for other infectious agents were unrevealing.

A diagnostic metagenomic analysis was performed on a brain-biopsy specimen from recipient 1. A nearly complete BoDV-1 genome was assembled (GenBank accession number, LT991983); the highest values of nucleotide identity were to a cluster of partial genome sequences of BoDV-1

Viral Proteins and Viral gRNA



Reporting of SAE / SAR in Germany

Agenda

1. **Definition of SAE /SAR and legal principles of SAE / SAR reporting**
2. **Donor-Derived infections (DDI) in Germany 2016-2023**
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5. **Conclusion**

Reporting of SAE / SAR in Germany

Conclusion

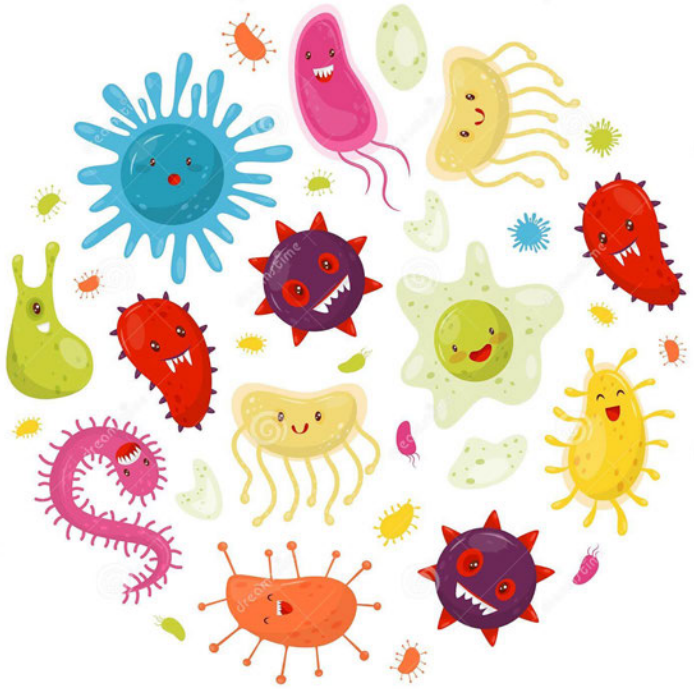
- Transmission of infections, infectious diseases or infectious pathogens important and obvious risk for organ recipients.
- DDI rate in our cohort low (0,21%), comparable with other countries.
- But: Significant mortality with 12 % in recipients with transmitted infections (p/p).
- Detailed and careful analysis of SAE and SAR cases may help to develop strategies to reduce the risk of transmitting donor disease to transplant recipients.

Reporting of SAE / SAR in Germany

Conclusion

- **European pilot study:**
  - established vigilance system in almost all participating countries (15/27)
  - low rate of serious adverse reactions
  - variability in definition of serious adverse events and serious adverse reactions
  - uniforme use of definition would be helpful
  - stay in contact and learn from each other, especially in very rare cases

Thank you for your attention!



www.fotolia.com/18540827/©Styf

Repository of policy and practice resources – bio-vigilance

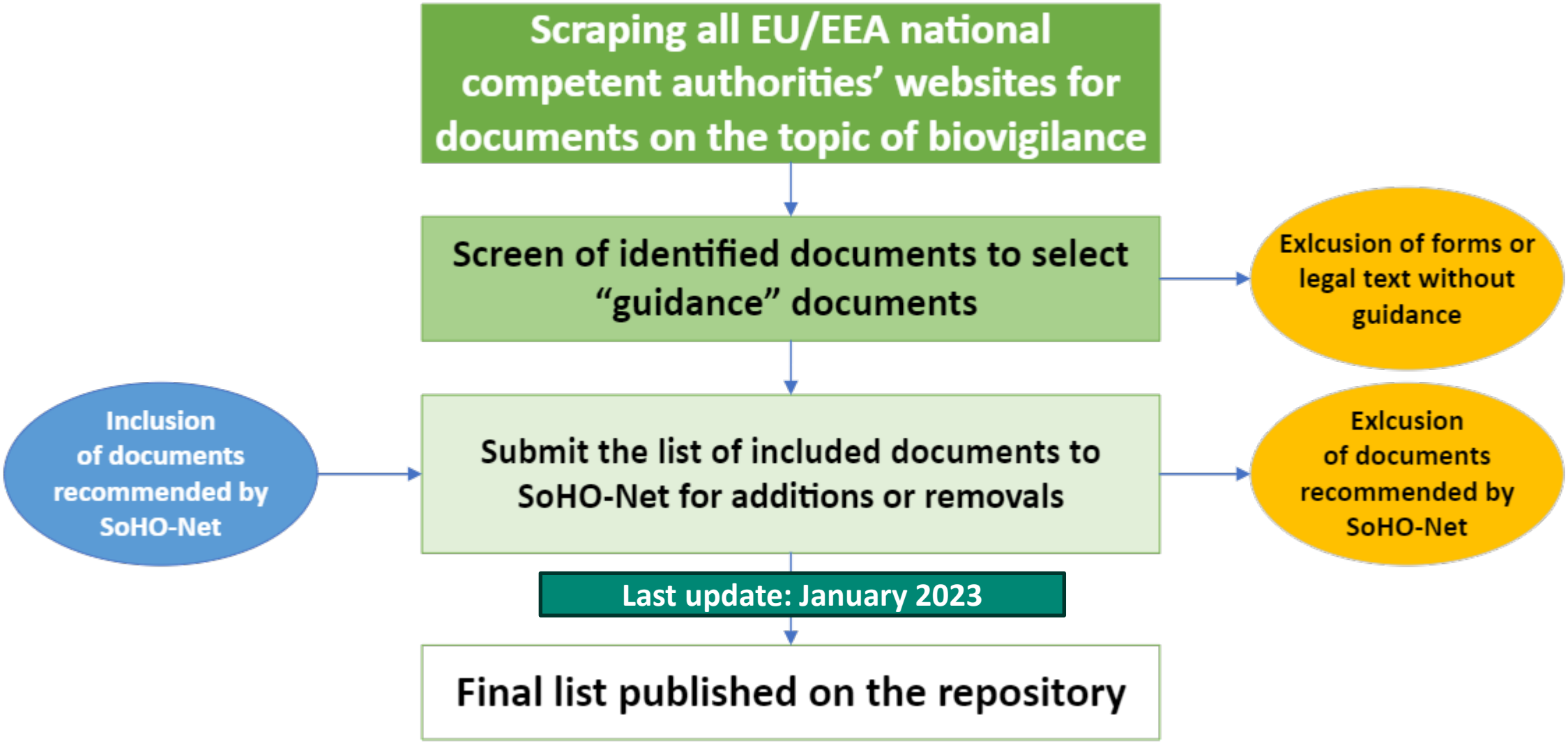
SoHO-Net Organs Group meeting – 19 June 2024

Aim

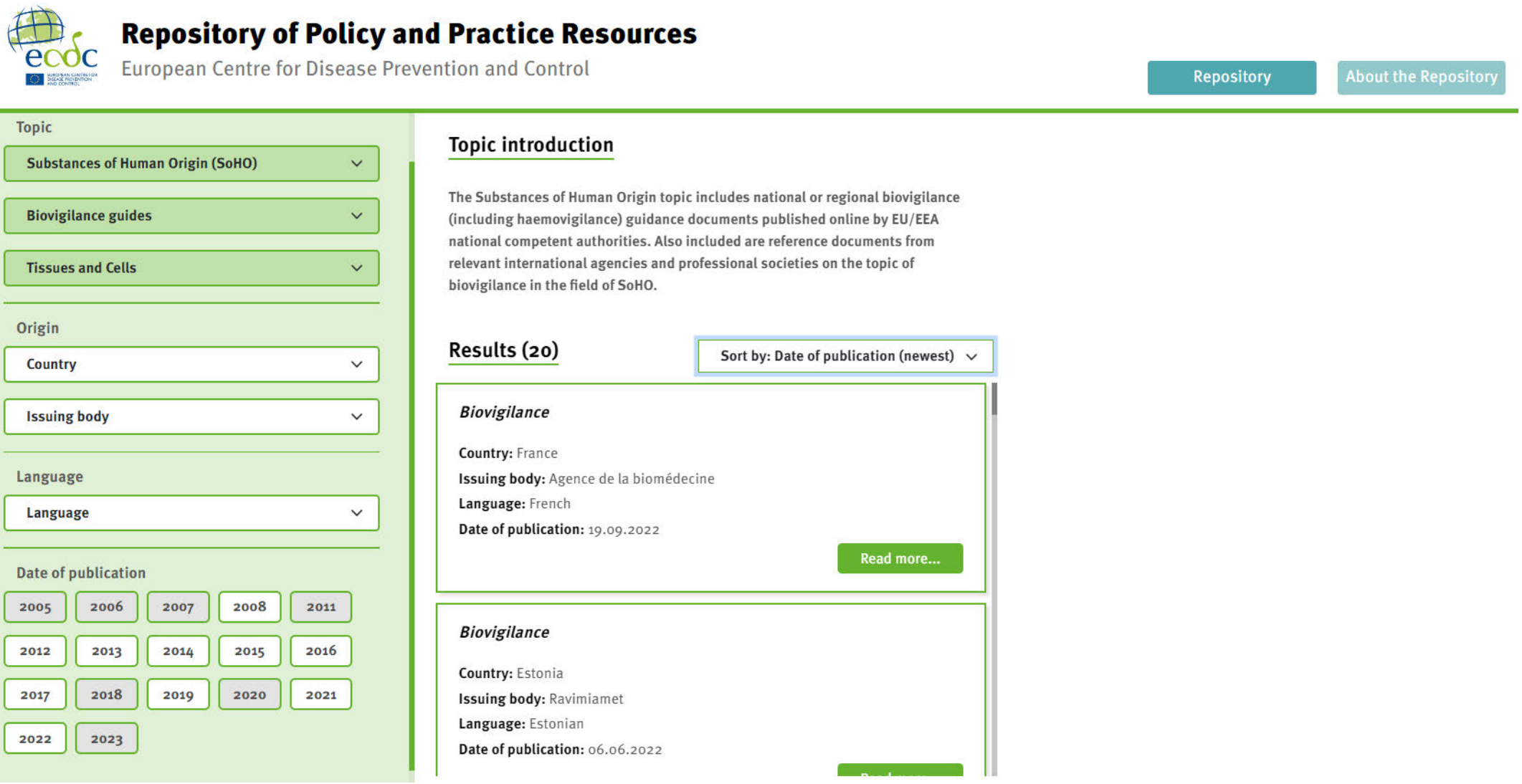
ECDC aims to set up a **repository of policy and practice resources** to facilitate and improve the sharing of such resources and expertise

This repository will cover different areas of relevance for ECDC.

Methods


Scraping all EU/EEA national competent authorities' websites for documents on the topic of biovigilance
Screen of identified documents to select "guidance" documents
Exlcusion of forms or legal text without guidance
Inclusion of documents recommended by SoHO-Net
Submit the list of included documents to SoHO-Net for additions or removals
Exlcusion of documents recommended by SoHO-Net
Last update: January 2023
Final list published on the repository

Repository


Repository of Policy and Practice Resources
European Centre for Disease Prevention and Control
Repository
About the Repository
Topic
Substances of Human Origin (SoHO)
Biovigilance guides
Tissues and Cells
Origin
Country
Issuing body
Language
Language
Date of publication
2005 2006 2007 2008 2011
2012 2013 2014 2015 2016
2017 2018 2019 2020 2021
2022 2023
Topic introduction
The Substances of Human Origin topic includes national or regional biovigilance (including haemovigilance) guidance documents published online by EU/EEA national competent authorities. Also included are reference documents from relevant international agencies and professional societies on the topic of biovigilance in the field of SoHO.
Results (20)
Sort by: Date of publication (newest)
Biovigilance
Country: France
Issuing body: Agence de la biomédecine
Language: French
Date of publication: 19.09.2022
Read more...
Biovigilance
Country: Estonia
Issuing body: Ravimiamet
Language: Estonian
Date of publication: 06.06.2022

SoHO page on the ECDC website

Related public health topics
Antimicrobial consumption
Antimicrobial resistance
Disease vectors
Healthcare-associated infections
Immunisation and vaccines
Microbiology
Migrant and refugee health
One Health
Prevention
Social and behavioural sciences
Substances of human origin
Surveillance resources

Substances of human origin

Translate this page

Substances of human origin (SoHO) is a term referring to a variety of biological materials that can be derived from the human body and are intended for clinical application. Broadly speaking, these are blood, tissues, cells, and organs, but they can be any parts of the human body, and secretions or excretions, collected from living or deceased persons.

SoHO are used as therapy for a wide range of medical conditions, and are sometimes the only available and lifesaving treatment. In other situations, the application of SoHO can significantly improve patients' quality of life.

Although very beneficial, SoHO are not without risks. To minimise these risks, the SoHO field is very carefully regulated in the EU. Among other bodies and organisations, ECDC is responsible for ensuring the quality and safety of SoHO. ECDC focuses on aspects of prevention of communicable diseases transmission that can come from SoHO donors.

https://www.ecdc.europa.eu/en/substances-human-origin

Repository

Read more

Repository of policy and practice resources - substances of human origin

This repository is a gateway to quality-assured policy and practice resources related to substances of human origin.

Access the repository

Network for the Microbial Safety of Substances of Human Origin (SoHO-Net)

ECDC's Network for the Microbial Safety of Substances of Human Origin (SoHO-Net) was established to facilitate cooperation between ECDC and European Union/European Economic Area (EU/EEA) Member States.

Read more

https://qap.ecdc.europa.eu/public/extensions/repository-ppr/repository-ppr.html

Thank you

Strongyloides stercoralis transmission through organs

– case reports –

Sophie Lucas Samuel, NFP, France

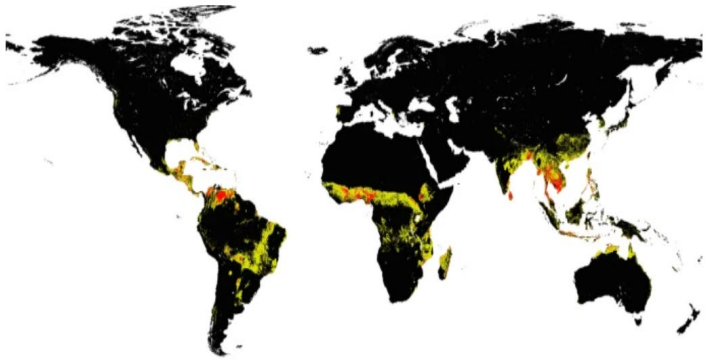
Morten Hagness, Oslo University Hospital, Norway

REMINDER ON THE STRONGYLOIDES STERCORALIS LIFE CYCLE

Duodenal nematode

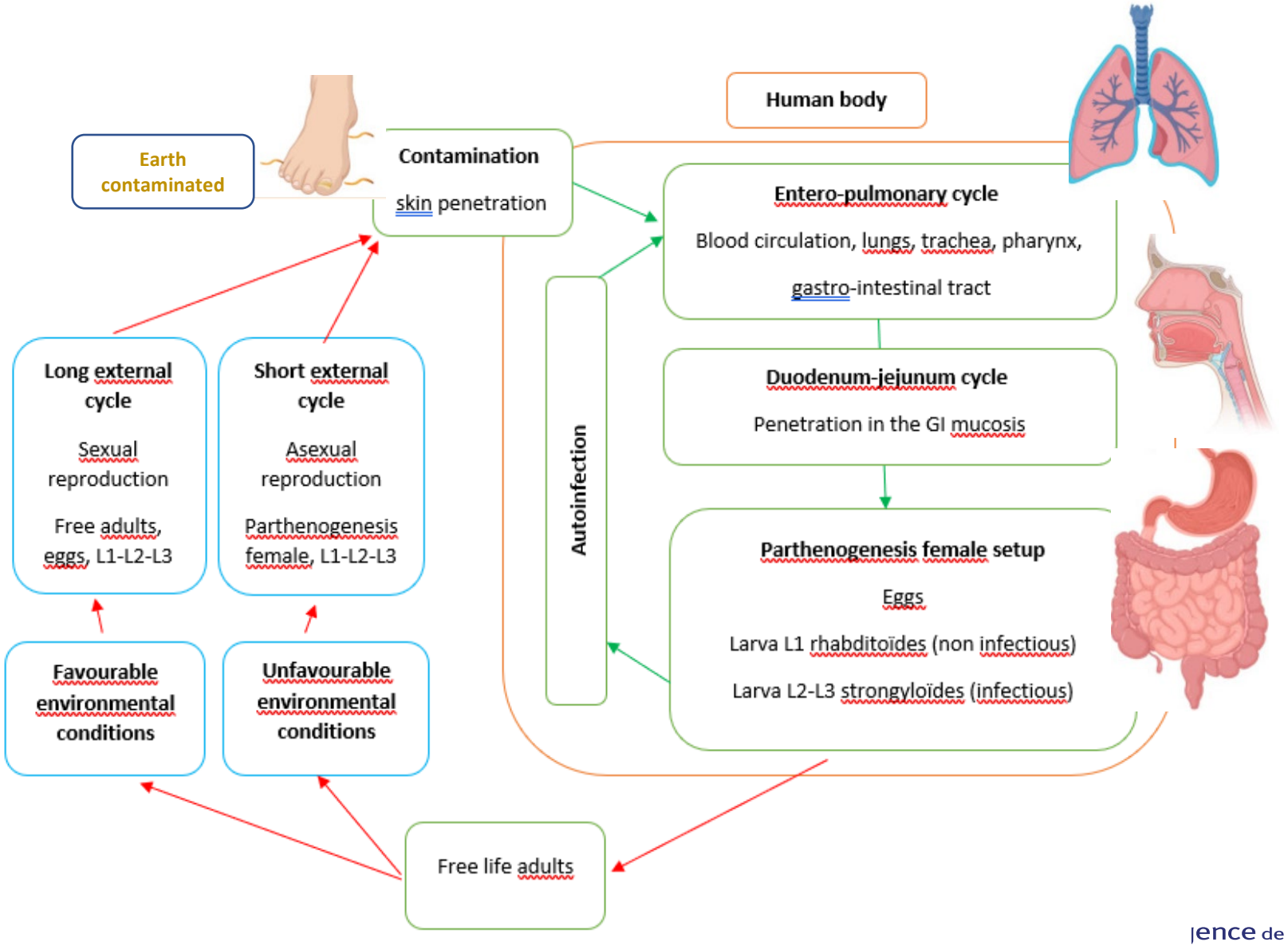
WHO / Strongyloides stercoralis threadworm in stool, analyze by microscope.

WHO more than 600 million people are infected worldwide



Fleitas and all 2022

Global map of prevalence of *S. stercoralis*, estimated with the ecological niche model



REMINDER ON THE STRONGYLOIDES STERCORALIS INFECTION

Anguillulosis in immunocompetent patients : Acute anguillulosis may evolve toward chronic anguillulosis if not treated

- 20-50% of cases are asymptomatic;
- Dissemination phase: 4 to 6 days;
- Clinical signs depend on severity and degree of infestation;
  - Rash at point of penetration (fleeting), transient allergic reaction;
  - Diarrhea associated with cutaneous manifestations (larva currens)
  - Blood hypereosinophilia : not systematically found (in 75% of the chronic cases)

REMINDER ON THE STRONGYLOIDES STERCORALIS INFECTION

Chronic anguillulosis in ~~the~~ immunocompromised patients: 2 forms associated with corticoids treatment, immunological disorder (notably HTLV infection) or immunosuppression

- Hyperinfectious anguillulosis :
  - Immune reconstitution syndrome (IRS)
  - Exacerbation of intestinal syndrome, absence of dissemination to other organs

- Disseminated anguillulosis : multivisceral syndrome that may evolve to maligne anguillulosis
  - Multivisceral larval dissemination
  - Digestive involvement (intestinal malabsorption, pseudo-occlusive syndrome),
  - Pulmonary involvement (cough, dyspnea, wheezing and/or hemotypsis, pulmonary infiltrate, ARDS),
  - Cardiac involvement possible
  - Secondary infection due digestive bacteria transported by larvae that migrate to tissue level
  - Death 60 to 80 % if not treated

REMINDER ON THE STRONGYLOIDES STERCORALIS INFECTION

Diagnosis

- History of living or travelling in endemic area
- Clinical: diarrhea associated with cutaneous manifestations (larva currens)
- Biology : hypereosinophilia (that may fluctuating in the chronic phase)
- Parasitology : direct diagnosis, stool examination = Coproculture
- Indirect diagnosis : serodiagnosis = ELISA, immunofluorescence

Treatment

- Common and hyperinfectious anguillulosis : Ivermectin: 2 courses at 3-week intervals depending on efficacy
- Disseminated anguillulosis : usually combines antiparasitic (Ivermectin+/-albendazole) and antibiotic therapy

REMINDER ON THE STRONGYLOIDES STERCORALIS INFECTION

Infection reported to organ recipients

- Origins of the infection to the recipient: donor-derived or reactivation of an unknown infection or de novo
- Frequency of post-transplant occurrence by organ: kidney > liver > heart > pancreas > lung / intestinal transplant
- Mortality> 50% due to increased risk of serious infection
    - Mortality appears to be higher when infection occurs early after transplantation (within 3 months) than when it occurs later (in endemic areas)
- Reactivation and donor-derived infection generally occur during the first three to four months post-transplant, when immunosuppression is the most intense

DESCRIPTION OF THE BIOVIGILANCE NOTIFICATION

Recipient of the right lung

21/09/21 : Graft of the right lung

19/10/21 : Good outcome, return home

26/10/21 : Cellular rejection treated with corticoids

12/12/21 : VRS pneumopathy

21/01/22 : Hospitalization for abdominal pain, vomiting, coughing and hemoptoic sputum

Additional examens:
- Bronchial fibroscopy: no visible bleeding
- Chest CT scan: ground glass on the right and pleural effusion
- NFS: hypereosinophilia 1100 /mm3

29/01/22: Deterioration of clinical condition leading to transfer to intensive care unit

BAL: haemorrhagic fluid containing numerous nematodes, suggesting pulmonary anguillulosis

31/01/22: Death of the lung recipient

19/04/22 : biovigilance notification

DESCRIPTION OF THE BIOVIGILANCE NOTIFICATION

Donor history

Travel to Réunion island in 2020

Recipient of the liver

4 months after the graft the recipient presented an acute respiratory failure and septic shock due to a disseminated anguillulosis leading to death

Recipients of the heart and recipient of the left kidney

Both treated with Ivermectin 4 months after the graft when the deaths of the liver and lung recipients were known.

Heart recipient : no sign of anguillulosis,

Left kidney recipient: increase of eosinophils just before Ivermectin treatment

Recipient of the right kidney

Detransplantation just after the graft for another reason

SEROLOGICAL RESULTS REGARDING THE STRONGYLOIDES STERCORALIS

Serological status of the donor			
	Positive	Negative	Not Know
Tests performed on pre-transplant samples			
Pre-graft serological status of the recipients			
Right Lung			
Liver			
Right Kidney			
Heart			
Left Kidney			
Pre-graft serological status of the recipients			
Right Lung			
Liver			
Right Kidney			
Heart			
Left Kidney			

Imputability to the graft was proved

agence de la biomédecine

FRENCH SYSTEM ORGANIZATION

SURVEILLANCE

French Public Health Agency

ECDC

ABM (Biovigilance)

alert

French High Council of Public Health (HCPH)

Competent authorities for Soho and Epidemiological surveillance

Members of HCPH commission in charge of infectious diseases

National referent center of the disease concerned

National operators for blood

Multidisciplinary expert group for SoHo securing

Virologists or parasitologists

Clinicians from Soho teams (procurement/graft)

Professionals comptent in ethic and economic domains

Patients representatives

Possible auditions of professionals, experts, patients ..

Opinion to the French Health Ministry

Recommandations disseminate to professionals in charge of donors selection and their biological qualification

agence de la biomédecine

PROPOSED MEASURES

No transmission has been reported from SoHo collected from living donors (organs, tissues, cells and blood)

For deceased donors:

- it is now mandatory to test all the donors, not only the ones who are coming, living or travelling from an endemic area.
- result of the serological test could be sent to clinical team in charge of the recipient within 10 days post graft;
- It is not mandatory to have them before the transplant

Rational:

- due to regular and frequent international travelling of the population, it may be difficult to trace historical data from deceased donors regarding this risk
- serological test is easy to performed, good sensitivity, reasonable price
- treatment is well tolerated with reasonable price

Results:

Positive (donor): the recipient is treated (after the graft) : Ivermectine : 200mg/kg at J1 and J4

: if the recipient is positive to HTLV 1: the duration of the treatment is increased

: if the recipient is coming from Africa (central or west) the search of a loasis with microfilaremia (sup to 2000/ml) is needed and if positive, the recipient is treated with Albendazole (400mg/kg during 3 consecutive days) (avoid encephalopathy linked to the intensity of filarial infection and massive release of parasitic antigens)

- A follow-up serology test should be carried out 1 month after the second course of treatment to verify the absence of infection.

Negative (donor): nothing to do

agence de la biomédecine

PROPOSED MEASURES

For all living organ donors :

- it is now mandatory to do a serological tests to all the donors, not only the ones who are coming, living or travelling from an endemic area.
- Positive result (donor): **the donor** is treated before donation : Ivermectine : 200mg/kg at J1 and J4  : if the donor is coming from Africa (central or west) the search a loasis with microfilaremia (sup to 2000/ml) is needed : the donor is treated with Albendazole (400mg/kg during 3 consecutive days) (avoid encephalopathy linked to the intensity of filarial infection and massive release of parasitic antigens)
- A follow-up serology test should be carried out 1 month after the second course of treatment to verify the absence of infection.

For all potential organ recipient :

- Before the graft, it is now mandatory to do a serological tests to all the potential recipient of an organ graft, not only the ones who are coming, living or travelling from an endemic area.
- Positive result: the patient is treated before the graft or re-treated if the donor is also positive

Donor-derived strongyloidiasis after organ transplantation in Norway

Donor:

Received: 9 July 2018 | Revised: 28 August 2018 | Accepted: 2 October 2018
DOI: 10.1111/tid.13008

SHORT COMMUNICATION

WILEY

Donor-derived strongyloidiasis after organ transplantation in Norway

Espen Nordheim[1,2] | Monica Olafsson Storrø[1] | Ane Kristine Natvik[3] | Grete Birkeland Kro[4] | Karsten Midtvedt[1] | Anna Varberg Reisæter[1] | Morten Hagness[1] | Børre Fevang[5,6] | Frank O. Pettersen[7]

Transpl Infect Dis. 2019;21:e13008.

- Young, previously healthy.
- Born in Thailand
- Living in west coast Norway for years, without any symptoms of Strongyloides infection.
- Pronounced dead (DBD) sept 2015
- Organs utilized: Kidney, simultaneous kidney and pancreas (SPK) and heart.

Recipient 1 54 Years old caucasian male

Kidney Tx 2015 CMV +/-

Induction: Basiliximab, methylprednisolon. Maintenance: Tx, MMF, Prednisone. Postop: No rejections or infections. S-Creatinin 100 µmol/L

Day 65: Readmission: Nausea, vomiting, diarrhea. Coloscopy: Inflammation CMV Colitis suspected. (antiviral treatment)

Septicemia, headache, no eosinophilia. Poynuclear cells in CBS.

Day 84: Gastric retention, larvae of Strongyloides in gastro-jeunal aspirate.

No travel history.

Ivermectin 200 µg/kg/day, subsequently albendazole. Immunosuppression altered from tac to CyA

No sequela and well-preserved graft function.

Recipient 2 36 year old old caucasian male

SPK 2015 CMV+/+

Induction ATG, Metylprednisolone. Maintainance: tac, MMF and prenisone.

No complications, excellent graftunction

Day 90: hospitalized with septicemia. CMV reactivation. Gastric retention and eosinophilia.

- Donor-duodenal biopsies revealed Strongyloides larvae

- Pre donation serum analysis donor showed Strongyloides IgG

Day 102: Albendazole 400 mg x2, ivermectin 200µg/kg. Immunosuppresion from tac to CyA

From day 112: Life – threatening GI –bleeding. 4 endoscopic procedures.

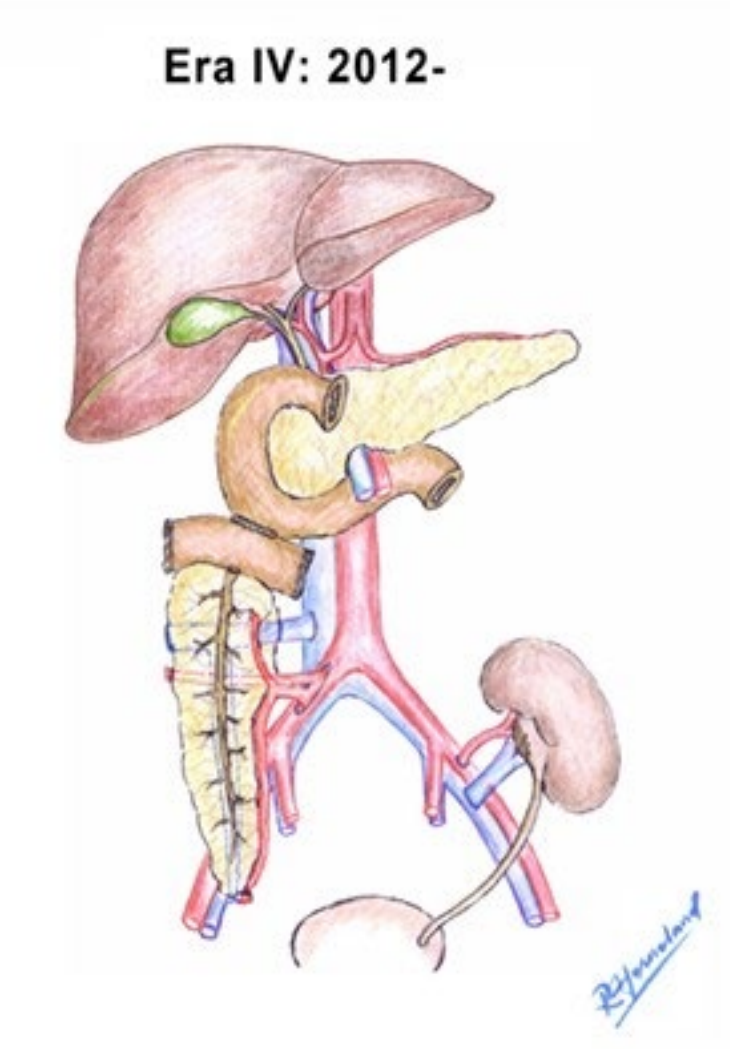
Day 116: Surgical resection of the duodenal segment.

Albendazole discontinued after 3 weeks, Ivermectin continued daily for 5 weeks, then once a month for 6 months.

Persisting IgG1/IgG4 positive. PCR in stool negative(2016/19/20/21/23)

PCR neg biopsies duodenum.

Good graftfunction. Never really recovered after infection/ transplant/reoperations



Recipient 3 50 Years old caucasian female

Heart transplant 2015

No eosinophilia, no severe infections

After donor testing: negative Strongyloides IgG

3 days of ivermectin 200 µg/kg

Remains asymptomatic

Oslo policy :

All donors serologically tested:

Test Result:	Clinical interpretation:
Negative	Negative
Grey-zone	Negative, unless from endemic area
Slightly positive	Positive
Positive:	Positive

Asymptomatic Patients:

- Stool Strongyloides PCR
- Serological testing
- After testing:

Ivermectin 200µg/kg/day for 3 days, repeat after 2 weeks.

Symptomatic Patients: Individualized treatment.

Results: ca 800 donors tested
Treated patients:

Year	ID	Organer	Comment	
2015	D186/15	Hear, Kidney, SPK	Thailand, Lved in norway for years	Recipients treated Disease in SPK, and kidney recipient
2017	D226/17	Liver, Kidney	Norwegian male 70	Recpients treated
2019	D93/19	Lungs, liver, kidney x2	Norwegian female 18	Recpients treated
2019	D207/19	Liver, kidneys x 2	Vietnamese male 62	Recpients treated
2021	D20/21	Lungs, liver, kidneys x2	Norwegian female 66	Recpients treated
2021	D129/21	Liver, kidneys x2	Polish male 53	Recpients treated
2021	D141/21	Liver, kidney x2	**Grey-zone, Vietnam**	Recpients treated
2021	D210/21	Liver, kidneysx2	Etnic Norwegian 74	Recpients treated
2021	D240/21	Kidneys x 2	**Grey-zone, Bulgaria**	Recpients treated
2022	D57/22	Liver, kidneys, Heart thomograft	Norwegian	Recpients treated
2022	D114/22	Llver	Norwegian female 61	Recpients treated

Patients not treated

Year	ID	Organer	Nationality, test	treatment
2023	D70/23		Norwegian Grey-zone	Not treated
2023	D80/23		Unknown origin, Grey-zone	Not treated
2023	D213/23	Liver, kidneys x2	Norwegian 75, Grey-zone	Not treated
2023	D201/23	Liver, kidneys x2	Norwegian male 52, Grey-zone	Not treated
2024	D42/24	Liver	Norwegian male 69, Grey-zone	Not treated
2024	D72/24	Kidneysx 2	Norwegian male 43, Grey-zone	Not treated
2024	D98/24	Hear, lungs, kidneys x2	Polish male 42, Grey-zone	Not treated

Thank you!

Sharing of information in EpiPulse
19 June

Session overview

Serious adverse reactions - reporting and sharing of experience

1. **EpiPulse and the role for the SoHO-Net Organs group** – Agoritsa Baka and Stefania De Angelis, ECDC
2. **Breakout session:** What events are of interest to share in EpiPulse for the SoHO-Net Organs group
3. **Discussion and reporting back from group discussions**

European Centre for Disease Prevention and Control

EpiPulse Event-Based Surveillance

Substances of human origin (SoHO)

Agoritsa Baka and Stefania De Angelis, ECDC

19 June 2024

Agenda

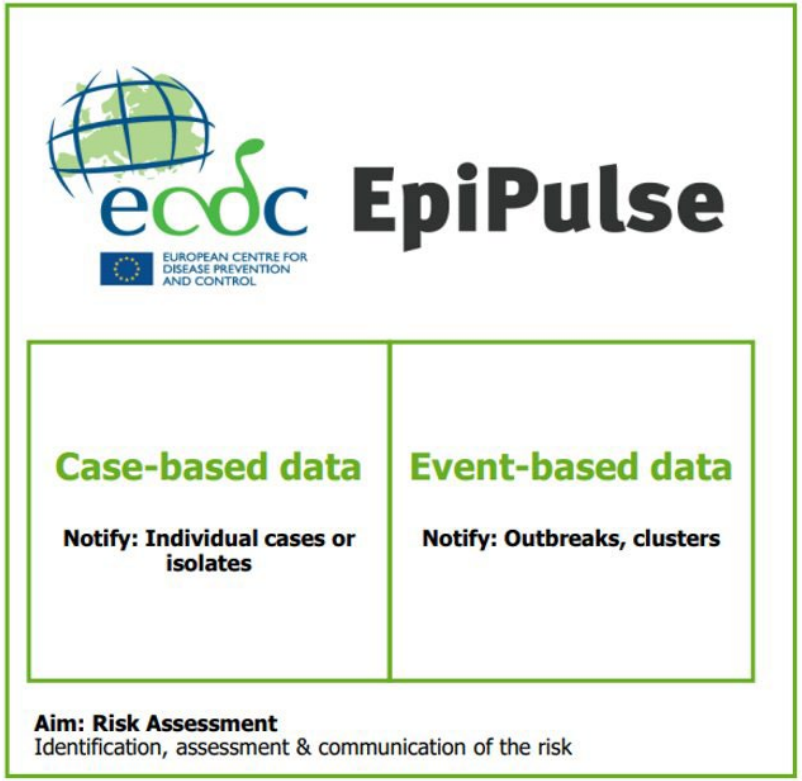
1. EpiPulse platform, its purpose and functionalities
2. Roles and responsibilities
3. Sensitive information
4. The platform
5. Next steps

The EpiPulse platform

What is EpiPulse? The European surveillance portal for infectious diseases

- Online portal for EU/EEA public health authorities, public health stakeholders and international partners
  - forum for information exchange and collaboration between countries
  - up-to-date-overview on potential cross-border threats to health
- Collect, analyse, share, and discuss data for **threat detection**, **monitoring**, **risk assessment** and outbreak response.

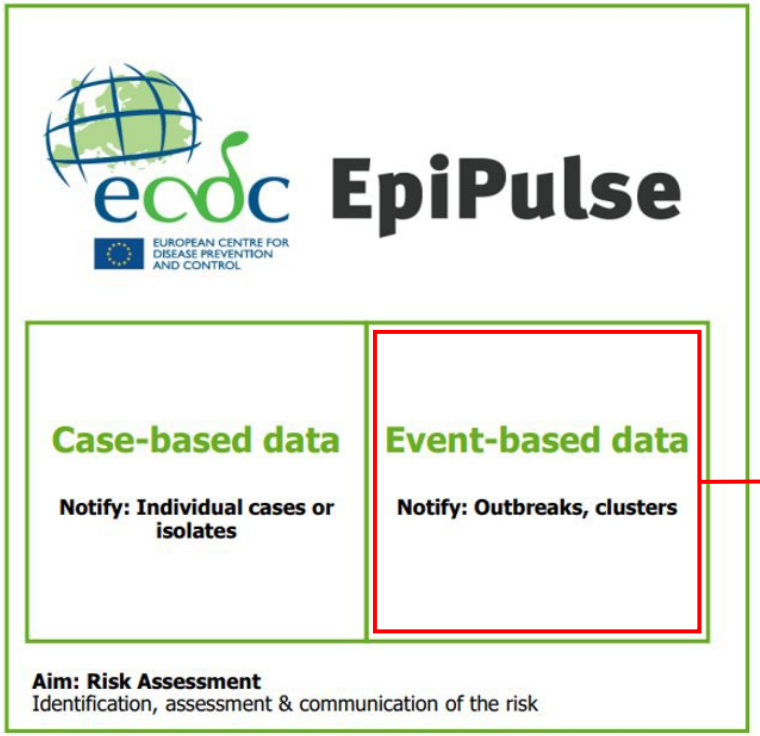
Integrates indicator-based and event-based surveillance, including molecular typing.



The regulation

Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health (**SCBTH**) and repealing Decision No 1082/2013/EU

Complies with the General Data Protection Regulation (**GDPR**)



Epidemiologic surveillance is the systematic collection, analysis and interpretation of data on communicable diseases to inform action
EU Dec 2018/945 ~60 diseases

Events, **Forum** and **News** sections launched in 2021

EpiPulse for the SoHO-Net

Receive information reported by ECDC and by other ECDC networks

- Up-to-date-overview on potential cross-border threats to health relevant for the SoHO networks
- Surveillance data on infectious diseases relevant to the SoHO networks

Information to be shared by the SoHO-Net in EpiPulse

- Events related to donor-derived communicable disease transmission through SoHO
- Events related to a communicable disease relevant to SoHO safety
- Sharing of experience and good practice related to SoHO donor selection

(To be discussed further with each SoHO-Net group)

Access to EpiPulse

- Public health stakeholders
  - EU/EEA countries
  - EU candidate and potential candidate countries
  - European Neighbourhood Policy countries
  - selected countries outside the EU/EEA that have agreed cooperation frameworks with ECDC [for specific domains]
- European Commission (DG-SANTE, DG-ECHO, DG HERA)
- Early warning and response system (EWRS) users
- EU Agencies (EFSA, EMA, EEA, ECHA, EU-OSHA)
- WHO-Regional Office for Europe

ECDC infectious disease networks

Each ECDC network has a domain in EpiPulse

- As ECDC **National Focal Points** for SoHO, you have access to the SoHO domain
- Different sub-networks in the SoHO domain:

o Blood
o Tissues and cells
o Human organs
o Medically assisted reproduction

Other users can be invited to specific events (when applicable):

WHO Euro
DG SANTE

You will receive only notifications related to events relevant to SoHO and your sub-network(s).
o upon creation of an event
o Only if you want, for new comments and other updates

	3- digit	Short name	Domain
1	ARH	ARHAI	Antimicrobial resistance and healthcare-associated infections
2	EIP	EI	Epidemic Intelligence
3	EVD	EVD	Emerging and vector borne diseases
4	FWD	FWD	Food- and waterborne diseases and zoonoses
5	HEP	HEP	Viral hepatitis
6	HIV	HIV	HIV/AIDS
7	IRV	IRV	Influenza and other respiratory viruses
8	LEG	LEGI	Legionellosis
9	PRE	PREP	Preparedness
10	SHO	SoHO	Substances of Human Origin
11	SRV	SRV	General Surveillance
12	STI	STI	Sexually transmitted infections
13	TUB	TB	Tuberculosis
14	VPD	VPD	Vaccine-preventable Diseases

EpiPulse items

There are different Item types to facilitate different activities within the platform:

- Signals
- **Events**
- Threats

Event-based surveillance

- [events under] Long-term monitoring
- Forum
- **News**

Event

- case(s)/cluster(s)/outbreak(s)/epidemiological situation(s)/incident(s)/public health risk situation(s)
- detected in/reported by one or several countries
- that according to your assessment pose (or may pose) a public health risk for the EU/EEA

Examples:

- a case of yellow fever imported from a country where the virus is not known to circulate
- an autochthonous case of a disease in the EU/EEA, where it has not been detected previously
- detection of a novel virus/disease
- first human case for the season of locally acquired West Nile Virus in the EU/EEA
- a human case of avian influenza infection
- an increase in the number of imported malaria cases in one EU/EEA country
- an increase of hepatitis E cases in one EU/EEA country

Role of ECDC assessment and Round Table

New EpiPulse Event → **ECDC assessment** → **ECDC Round Table review** → **Follow-up actions**

- Review Event post and responses from other countries
- Follow-up with countries
- **Situation Awareness Summary**
  - restricted version
  - public version

- Review Event and classification
  e.g. Event → **Threat**
  SCBTH criteria
- Open to relevant stakeholders
  e.g. WHO EURO, EFSA

- Follow-up with countries
- Situation Awareness Summary included in CDTR
  - Daily **restricted**
  - Weekly **restricted**

  } EpiPulse *
  - Weekly **public** — ECDC website

* Access to daily/weekly restricted CDTR is limited to nominated Epidemic Intelligence and Preparedness domains

What information can be shared further

- ✓ **Only personal account to access EpiPulse – no generic email**
- ✓ **Info cannot be shared further, unless ECDC agrees following request**

Terms of Service - Purpose and legal basis of EpiPulse

The purpose of EpiPulse is to support infectious disease surveillance, early threat detection and risk assessment in the European Union/European Economic Area (EU/EEA). The web-based platform is designed for collecting, retrieving, exploring, exchanging and discussing data and information on cases of infectious diseases, pathogens and signals and events posing potential threats to public health in Europe and beyond. EpiPulse brings together nominated national experts from EU/EEA and non-EU/EEA countries, ECDC staff and representatives of other European authorities and international organisations.

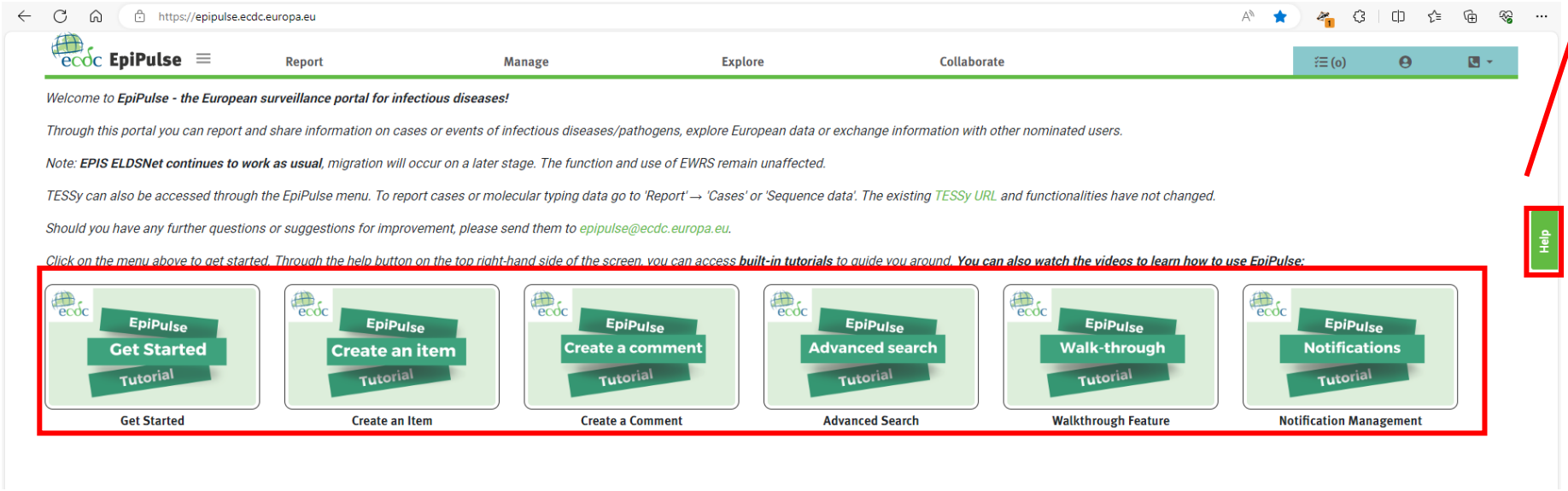
The legal basis for this activity is Regulation (EC) No 851/2004 (ECDC's Founding Regulation), in particular articles 3, 4, 8, 10 and 11, and Decision 1082/2013/EU on serious cross-border threats to health.

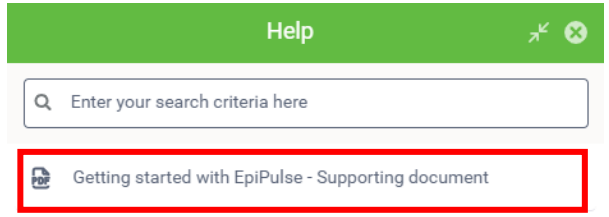
Confidentiality
As a User, I hereby declare that:
1. I will use EpiPulse only for the purposes and within the legal framework described in art. 1 above.

Please treat the data in the platform as sensitive non-classified unless specifically indicated as public

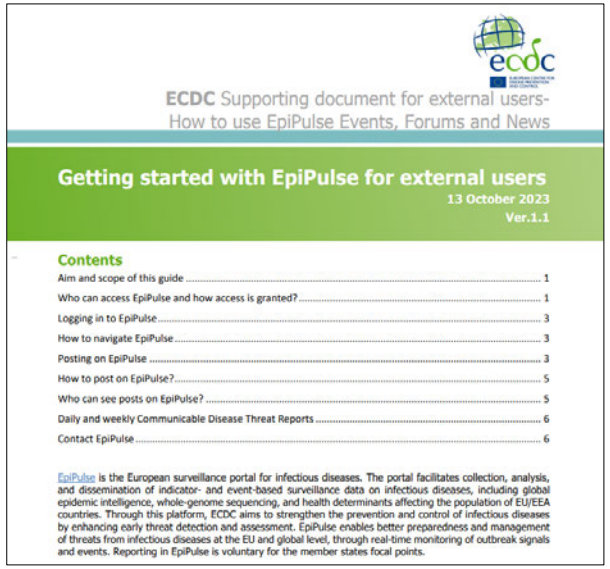
The platform

Homepage, instructional videos, help and support docs

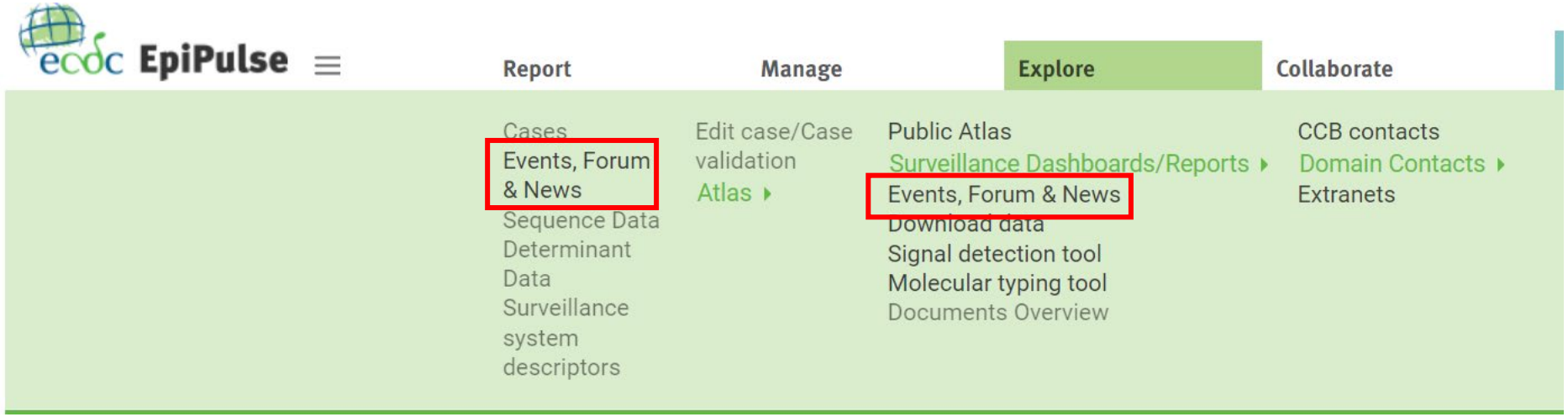




Help



Main menu



Events list

ID	Participating domain	Type	Title	Created by	Pathogens	Diseases	Modified time	Flags
2024-EIP-00027	TALD, ARHAI, HIV, FWD, EVD, SoHO, HEP, VPD, TB, IRV, STI, LEGI, EI, PREP	Event	Mass gathering monitoring - Hajj - Kingdom of Saudi Arabia - 2024	ECDC/Public Health	Not applicable	Not applicable	2024-06-14 14:01	
2024-EVD-00019 (new)	SoHO, EI, EVD	Event	Increasing risk for autochthonous dengue transmission in the EU	ECDC/Public Health	Dengue virus	Dengue	2024-06-10 15:38	
2024-EVD-00018	EI, SoHO, EVD	News	Seasonal surveillance on West Nile virus infections starts in week 23	ECDC/Public Health	West Nile virus, not specified	West Nile virus infection	2024-06-07 14:00	
2024-EIP-00026	SoHO, EVD, EI, PREP	Event	Increase in cases of confirmed DENV infection with exposure in	Italy/Public Health	Dengue virus	Dengue	2024-06-07 13:57	

Event details

Item details

View access settings | ‹ Previous | Next ›

ID:	2024-PRE-00001	Type:	Event	Title:	Increases in parvovirus infections
Diseases:	Not applicable	Pathogens:	Not applicable	Participating domain:	**EI**, FWD, IRV, PREP, SoHO

Help

⊞ Key information

⊞ Document workspace (contains 1 files in 1 spaces)

Situation Awareness | Comments | Links | Outputs | Visualisations | ECDC

Summary (posted) (Modified time: 2024-06-06 11:19)

View Posted Summary | Edit summary | Show differences

	(posted)	(posted)
Executive Summary	• An increase in the number of parvovirus B19 infections has been recently reported by Denmark, Ireland, Lithuania, the Netherlands, Norway, Latvia, Czechia and France. • Although a detailed epidemiological analysis is lacking due to the disease not being under surveillance in most countries, the data	• An increase in the number of parvovirus B19 infections has been recently reported by Denmark, Ireland, the Netherlands, Norway and France. • Although a detailed epidemiological analysis is lacking due to the disease not being under surveillance in most countries, the data

Notifications

EpiPulse: 2024-EIP-00019-Item created by ECDC -EWRS - Parvovirus B19 infections

N noreply@ecdc.europa.eu
To Stefania De Angelis

[Notice]: This is an external email. Be cautious when clicking links or opening attachments. When in doubt, contact Front Office.

Dear Stefania De Angelis,

The following update or item creation has taken place in EpiPulse:

- 2024-EIP-00019 - EWRS - Parvovirus B19 infections (Threat) - (created by EI, ECDC, Public Health), Item created

To modify your notifications preferences, please visit the My profile: General page.

Kind regards,
ECDC's EpiPulse Team

EpiPulse contact email: epipulse@ecdc.europa.eu

Next steps

September

- EpiPulse hands on training and workshop, more information will follow.
- You will be able to communicate and report events in EpiPulse after the hands-on training.

Thank you!

Questions?

- General EpiPulse feedback and technical issues - EpiPulse@ecdc.europa.eu
- Access support or login questions - Country.Cooperation@ecdc.europa.eu
- For SoHO specific content in EpiPulse - Soho@ecdc.europa.eu

EpiPulse for the SoHO-Net

Receive information reported by ECDC and by other ECDC networks

- Up-to-date-overview on potential cross-border threats to health relevant for SoHO
- Surveillance data on infectious diseases relevant to SoHO

Information to be shared by the SoHO-Net in EpiPulse

- Events related to donor-derived communicable disease transmission through SoHO
- Events related to communicable disease relevant to SoHO safety
- Sharing of experience and good practice related to SoHO donor selection.

Breakout session: what events are of interest to share in EpiPulse for the SoHO-Net Organs group

You will be divided into 5 groups with one facilitator per group to guide you. Each group you will:

1. Discuss which event that you find would be relevant to share in EpiPulse related to
   I. donor-derived communicable disease transmission through SoHO
   II. communicable disease relevant to SoHO safety

2. Discuss what kind of experience and good practice related to SoHO donor selection that you find would be relevant to share in EpiPulse.

Try to be as specific as possible, you are welcome to give examples.
Summarize your discussion and conclusions in bullet points and nominate one or two persons who will present the summary of the discussions, orally or with slides.

Each group will have 5 minutes for their presentation, followed by a common discussion. The proposed topics will be discussed again at the EpiPulse hands-on training for network members in September.

Session 8
Emerging diseases
19 June

Session overview

Emerging diseases – overview and trends

1. **Emerging vector-borne diseases in EU/EEA – Overview and trends and available surveillance tools** – Celine Gossner, ECDC
2. **Questions and answers** – All
3. **Proposal for a repository for guidance on emerging diseases and organ transplantation** – Francois-Xavier Lamy, ECDC
4. **Discussion** – All

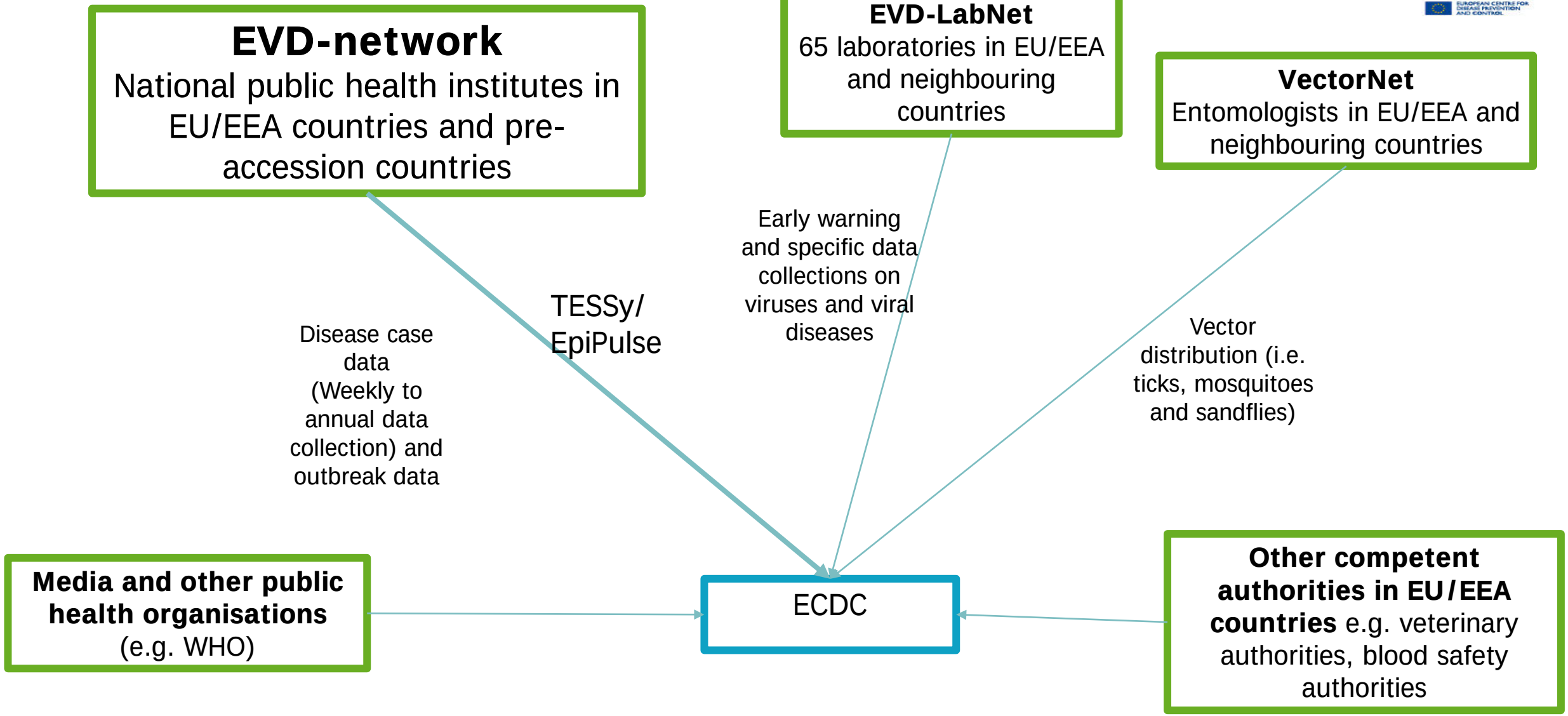
European Centre for Disease Prevention and Control

Vector-borne diseases in EU/EEA – Overview, trends and available surveillance tools

Céline Gossner, Principal Expert Emerging and Vector-Borne Diseases / Group Leader Emerging, Food and Vector-Borne Diseases, Celine.Gossner@ecdc.europa.eu

SoHO-Net Organs meeting, 18-19 June 2024

Data sources, not exhaustive

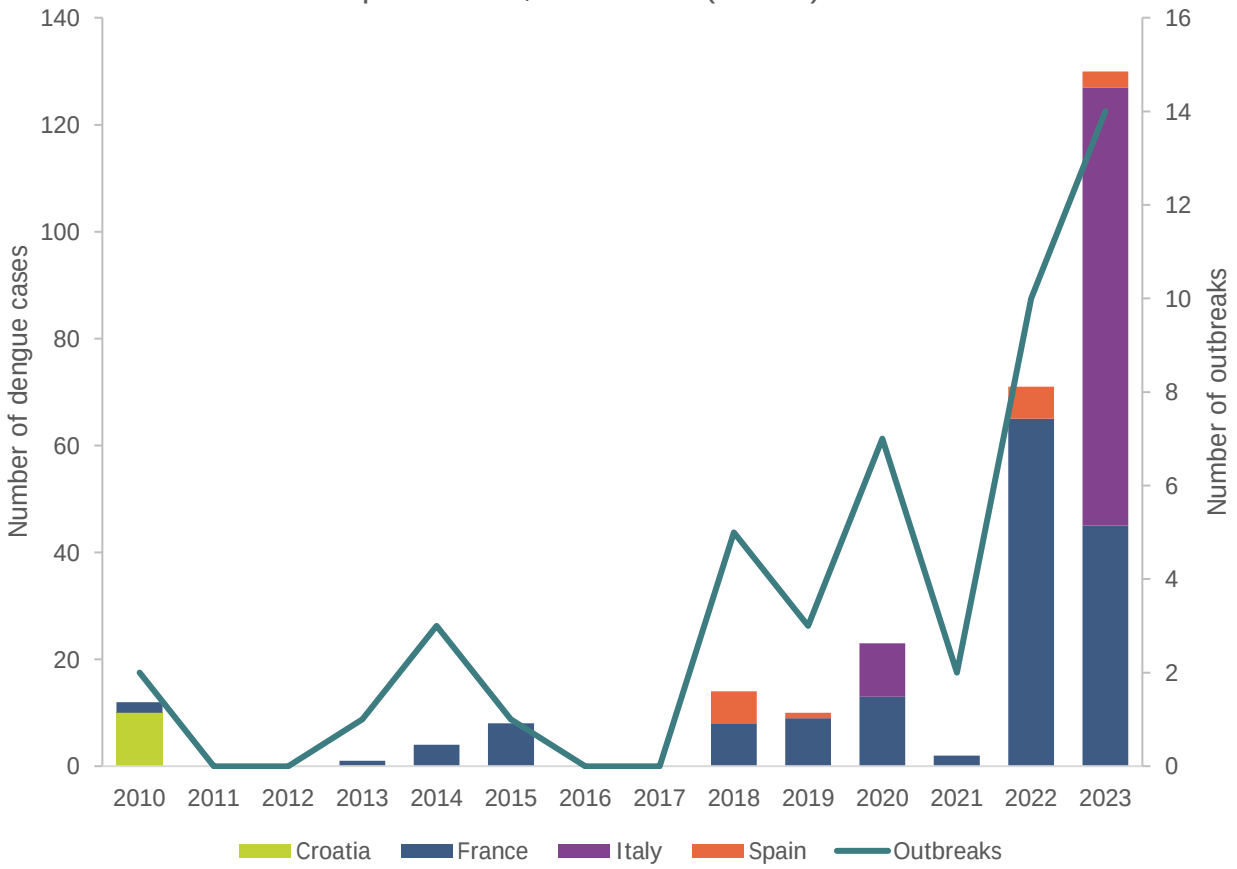


Dengue

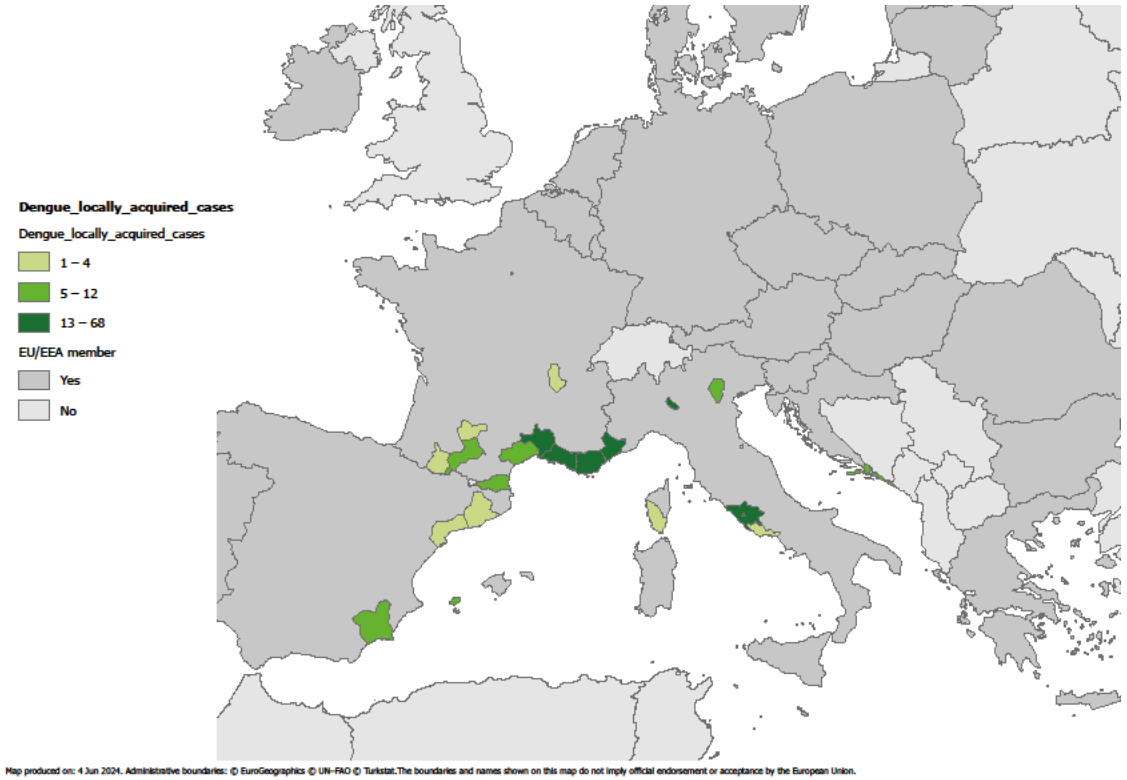
- Transmitted among humans by *Aedes aegypti* (yellow fever mosquito) and *Aedes albopictus* (Asian tiger mosquito)
- ¼ people infected with dengue virus will get sick
- On average 2,300 cases per year in Europe; >99 % are imported
- While autochthonous outbreaks are occurring within continental Europe, the disease is NOT considered endemic.

Overview of the dengue situation in the EU

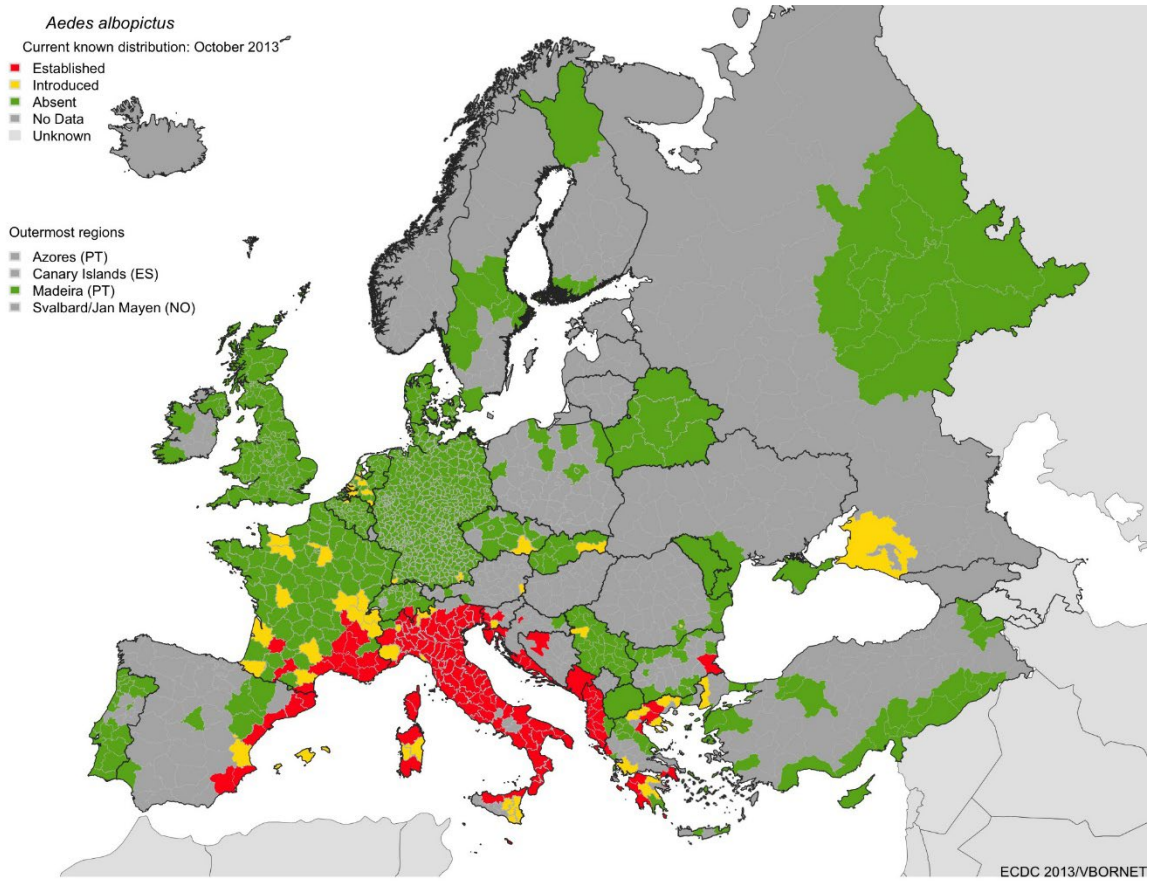
Number of locally-acquired dengue cases and outbreaks in the European Union, 2010-2023 (n=275)



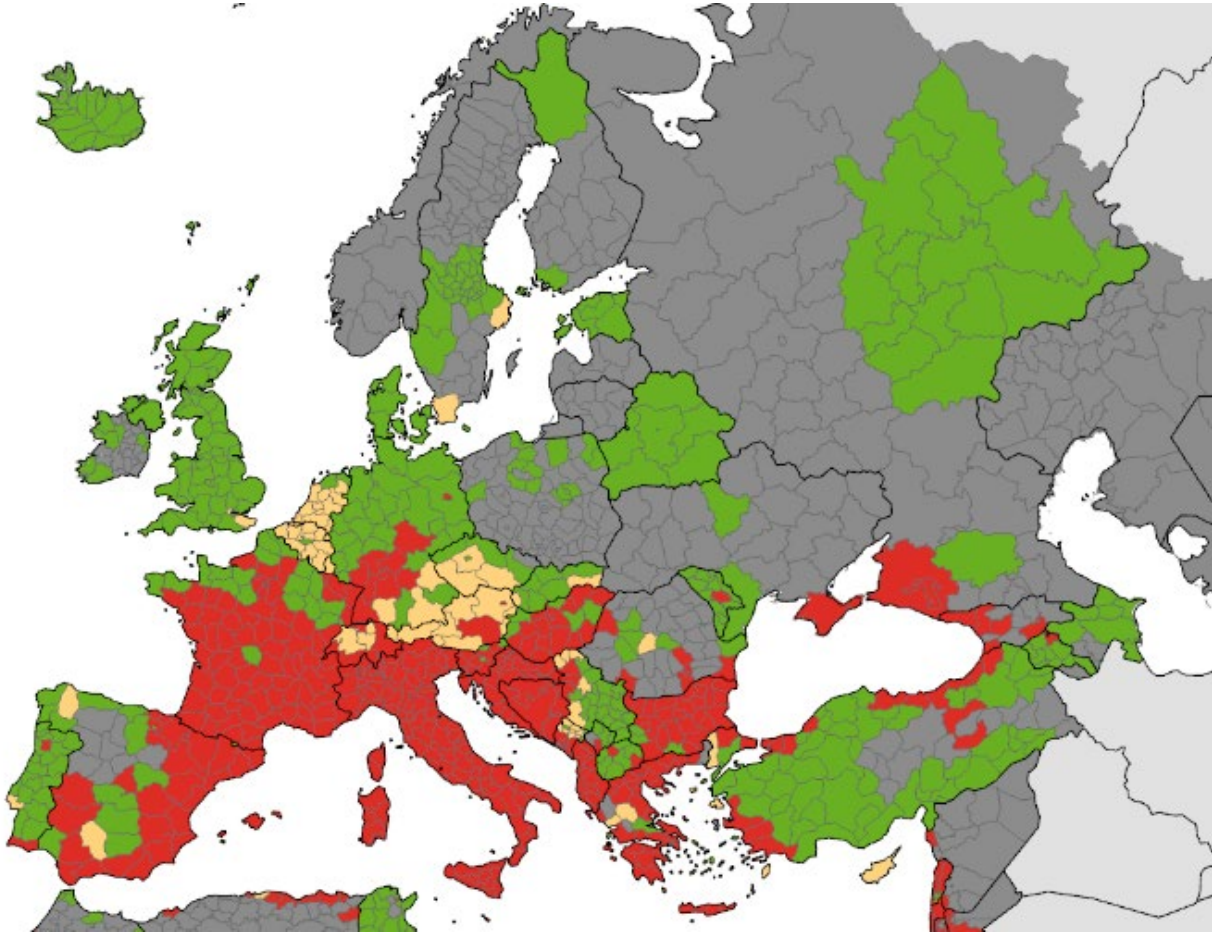
Number of locally-acquired cases of dengue per region, 2010-2023



Spread of *Aedes albopictus*

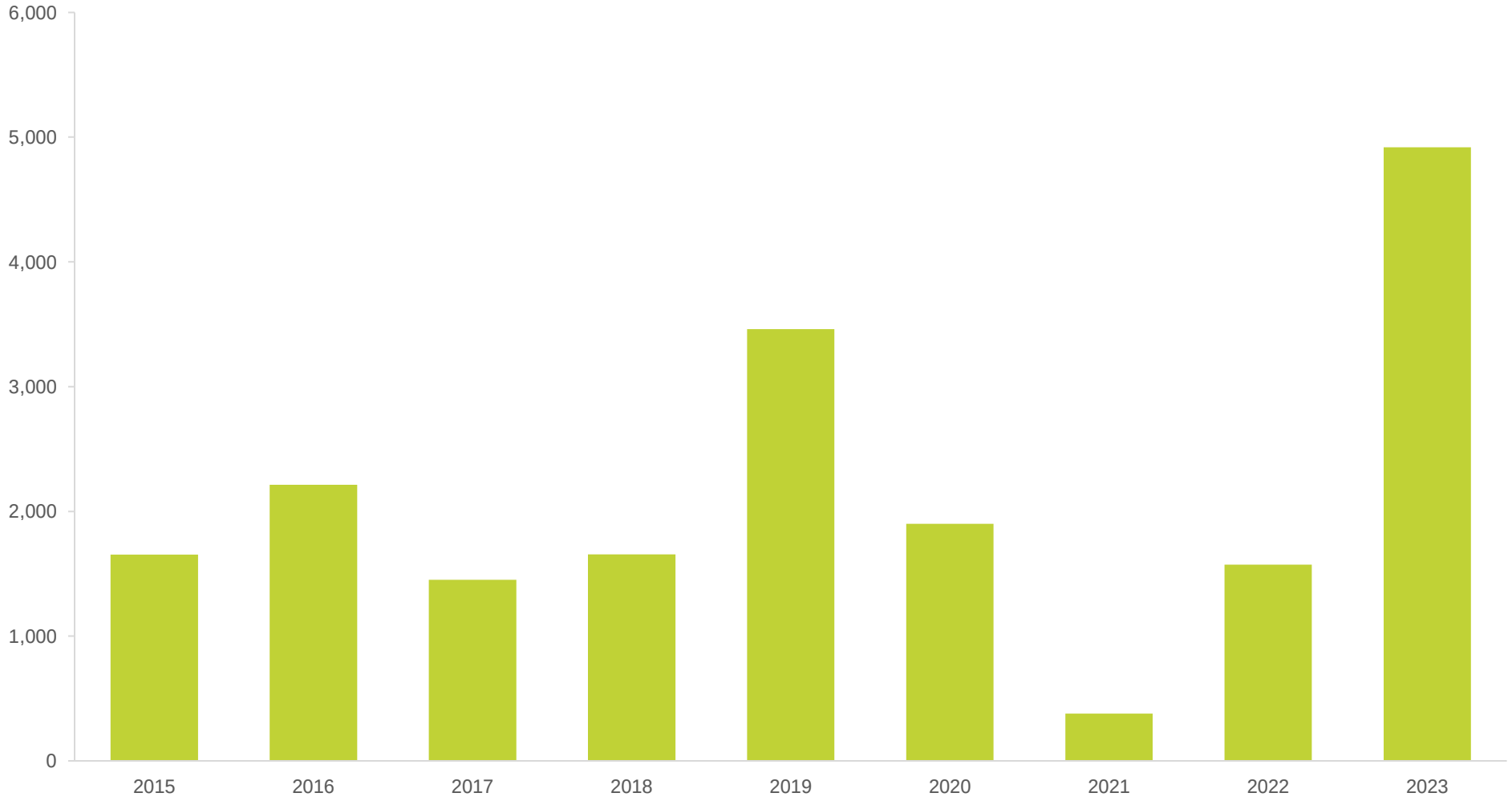


May 2014



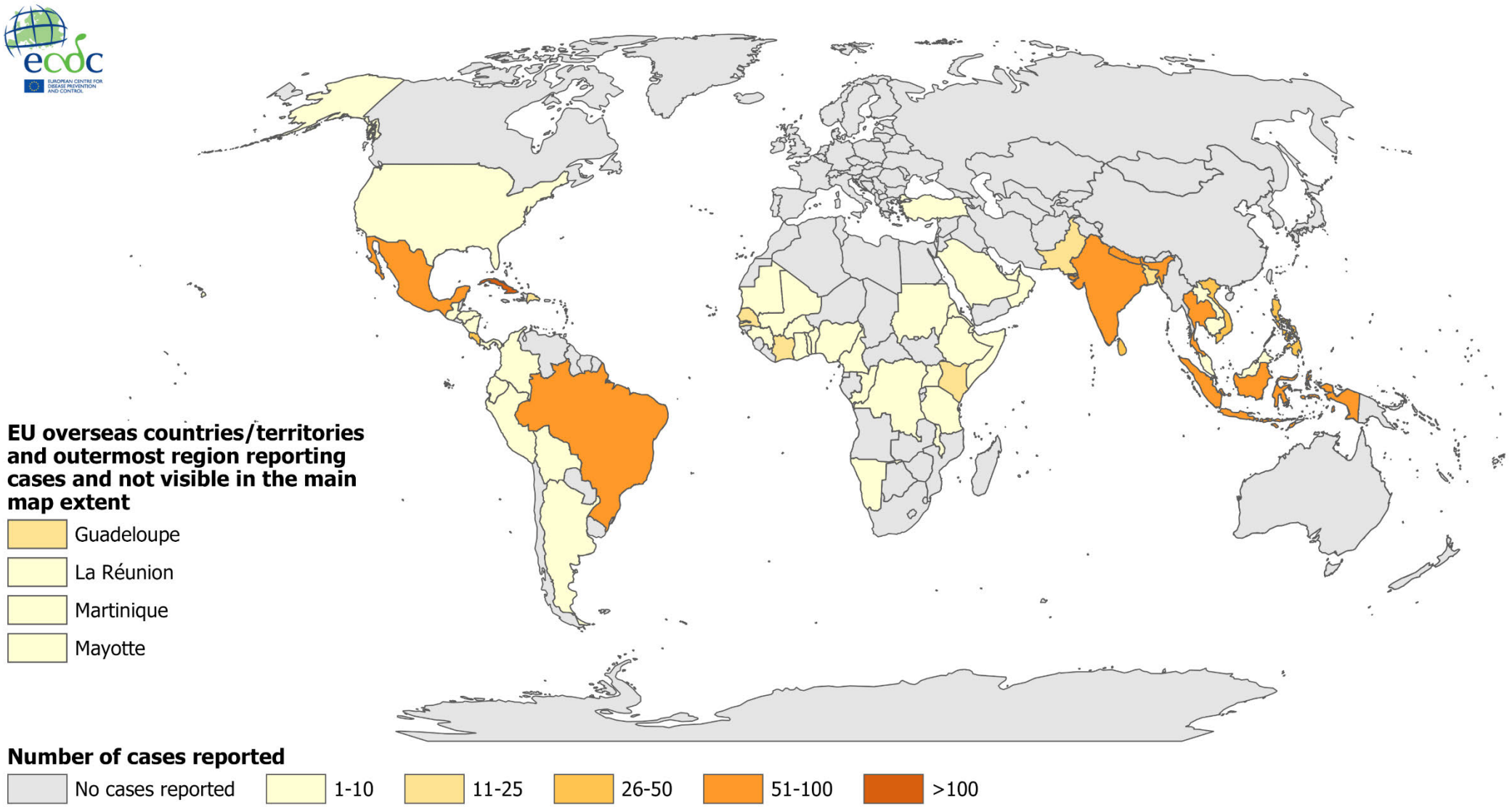
May 2024

Imported cases of dengue reported in the EU/EEA, 2015-2023*



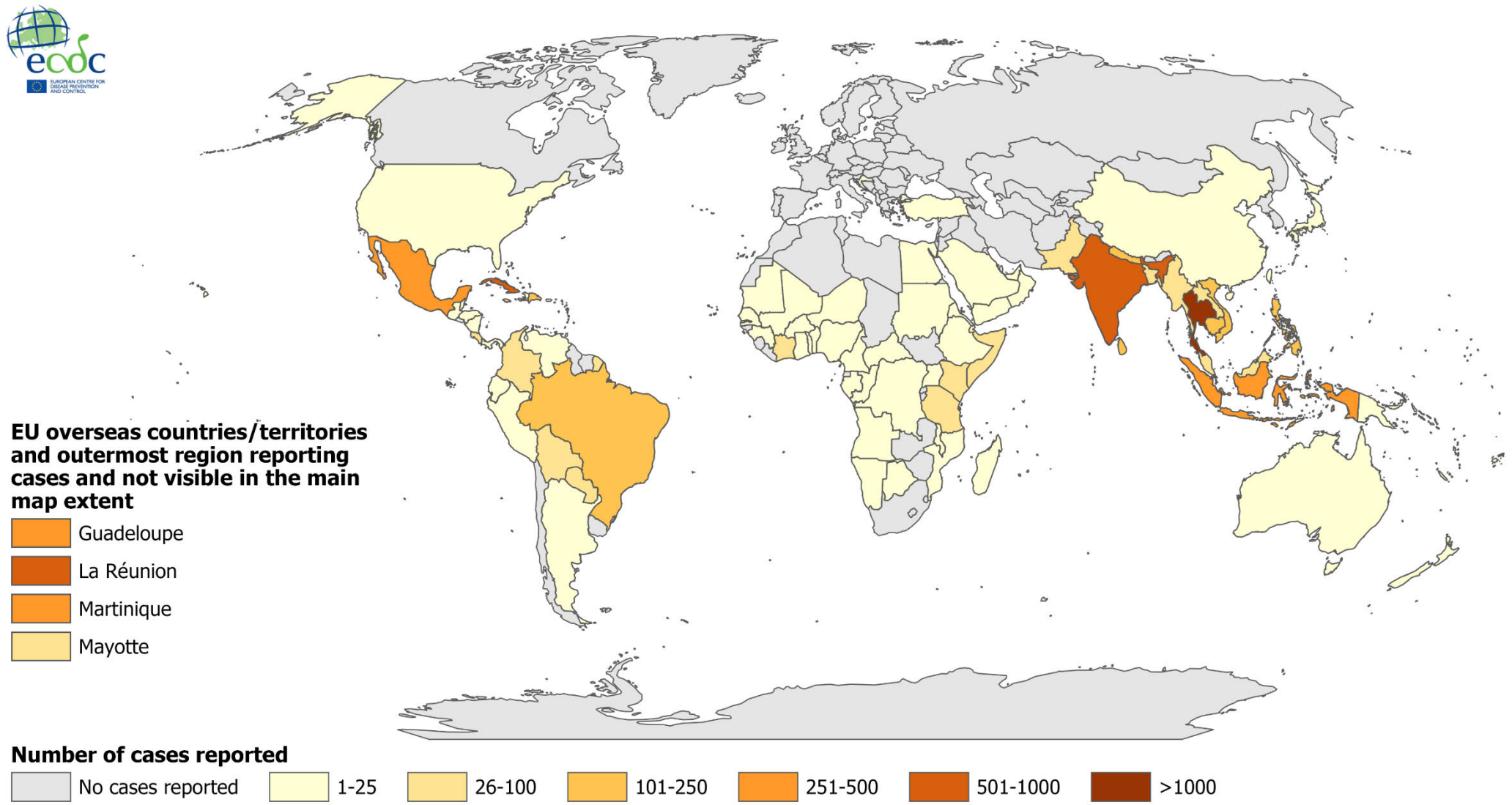
*preliminary data for 2023

Place of infection of imported cases of the dengue to the EU/EEA, 2022

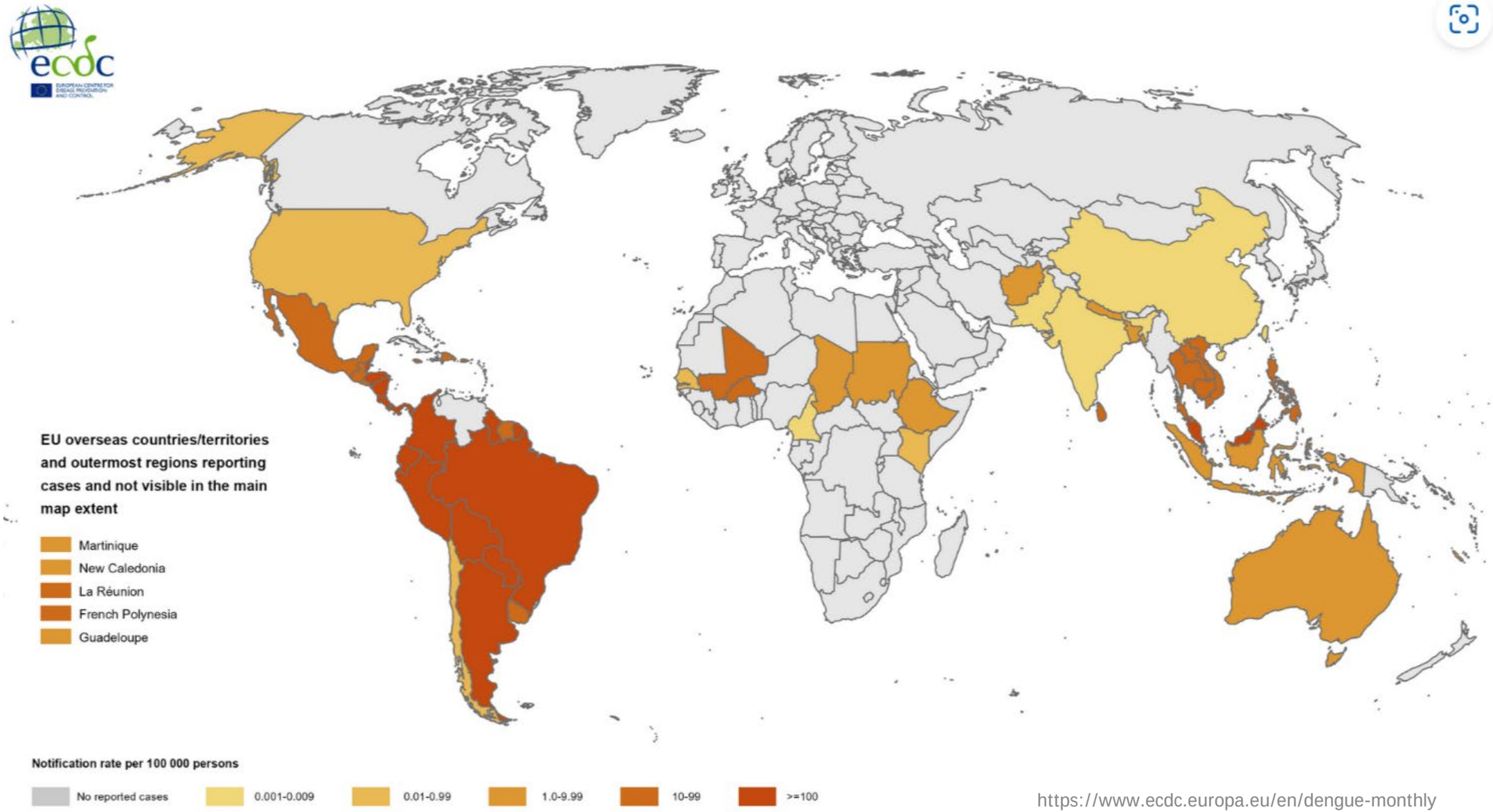


Administrative boundaries: © EuroGeographics ©UN-FAO. The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. Map produced by ECDC on 05 June 2024.

Place of infection of imported cases of the dengue to the EU/EEA, 2018-2022



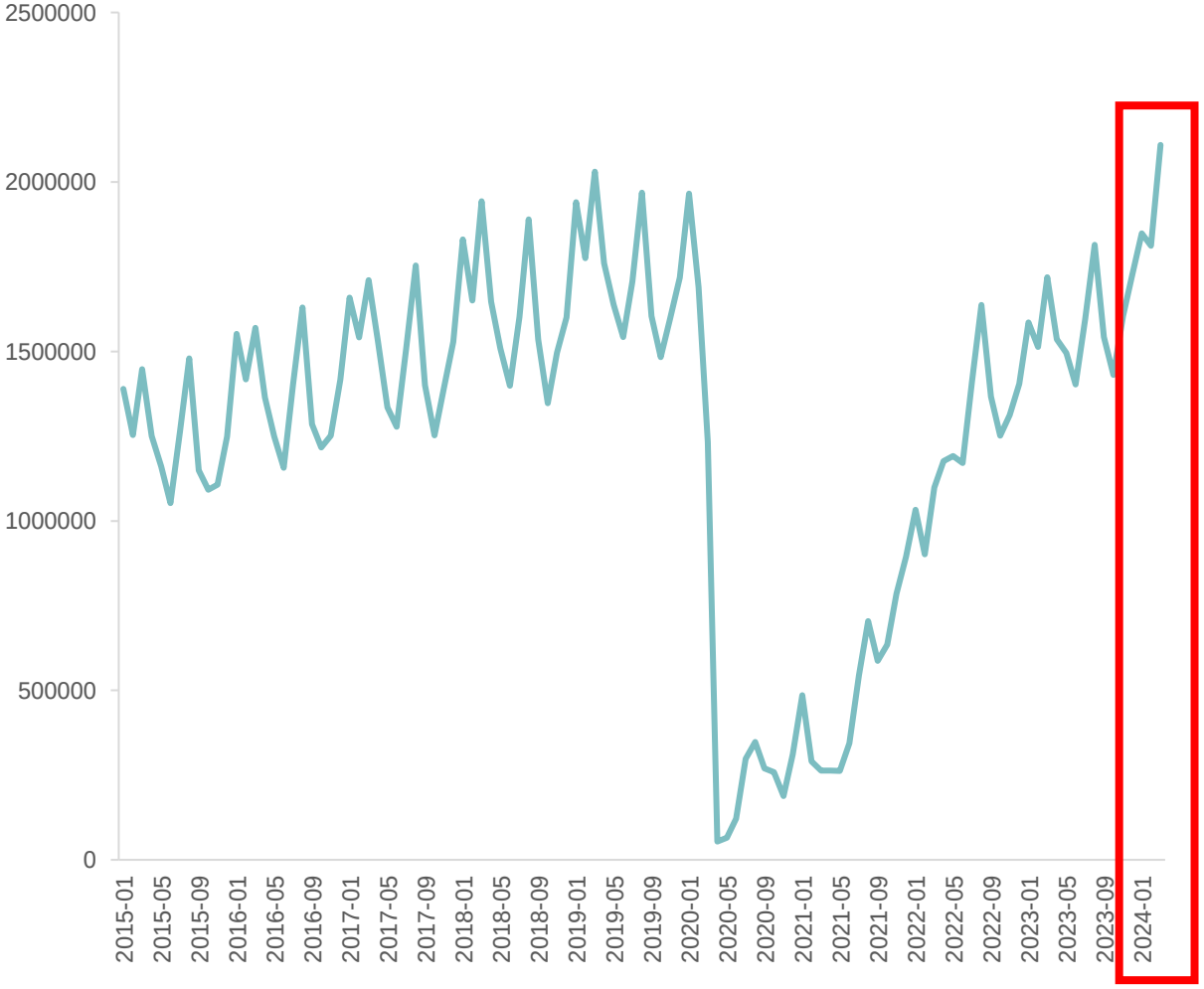
Notification rate of dengue, per 100 000 population, Feb-Apr 2024 (as reported by countries)



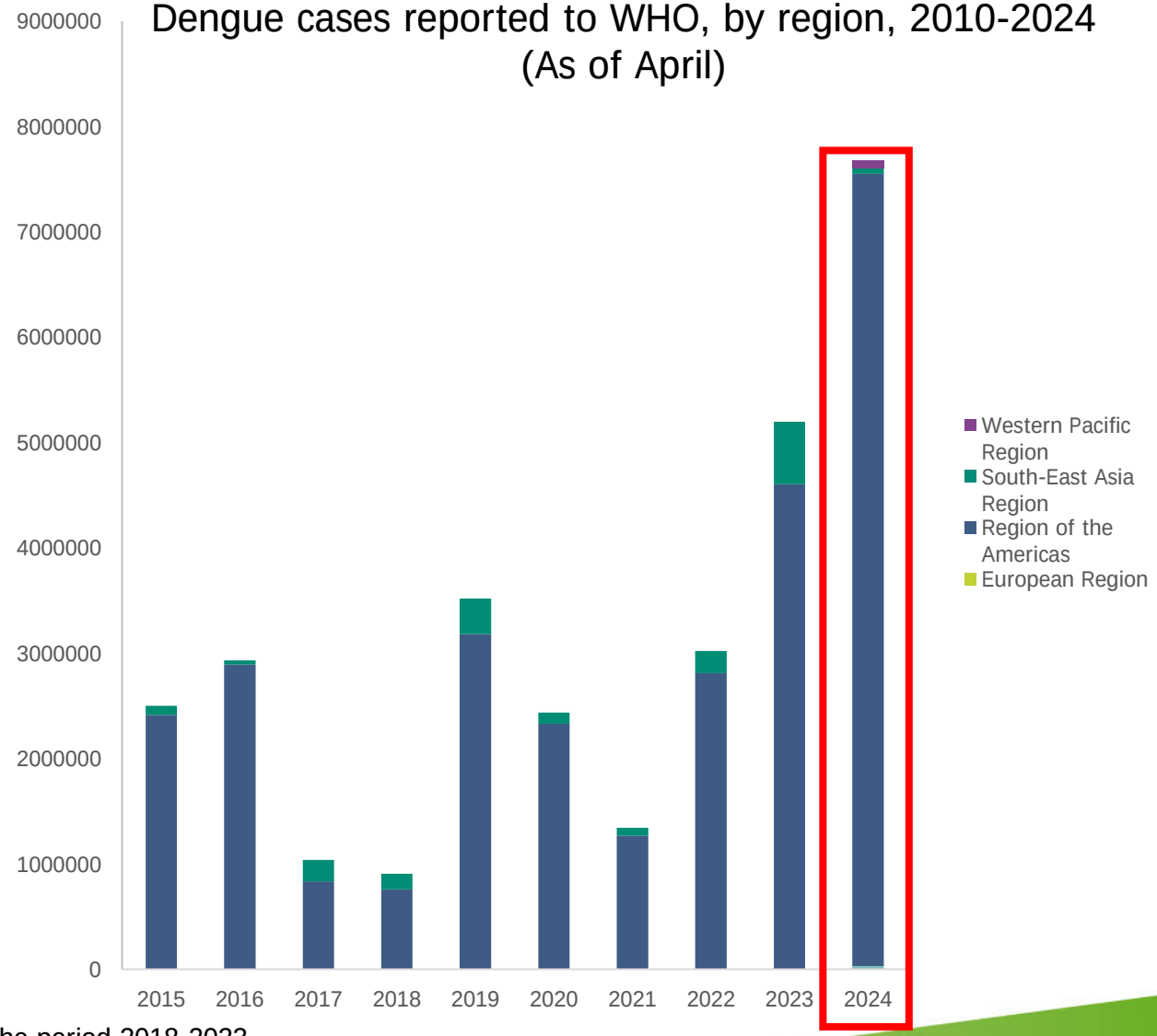
https://www.ecdc.europa.eu/en/dengue-monthly

Risk of dengue importation into Europe, 2024

Flight passengers arriving to the EU/EEA from selected dengue endemic countries*, 2015-2024 (As of March)



Dengue cases reported to WHO, by region, 2010-2024 (As of April)



*20 countries of infection from where the most travel-related cases were reported in TESSy for the period 2018-2023

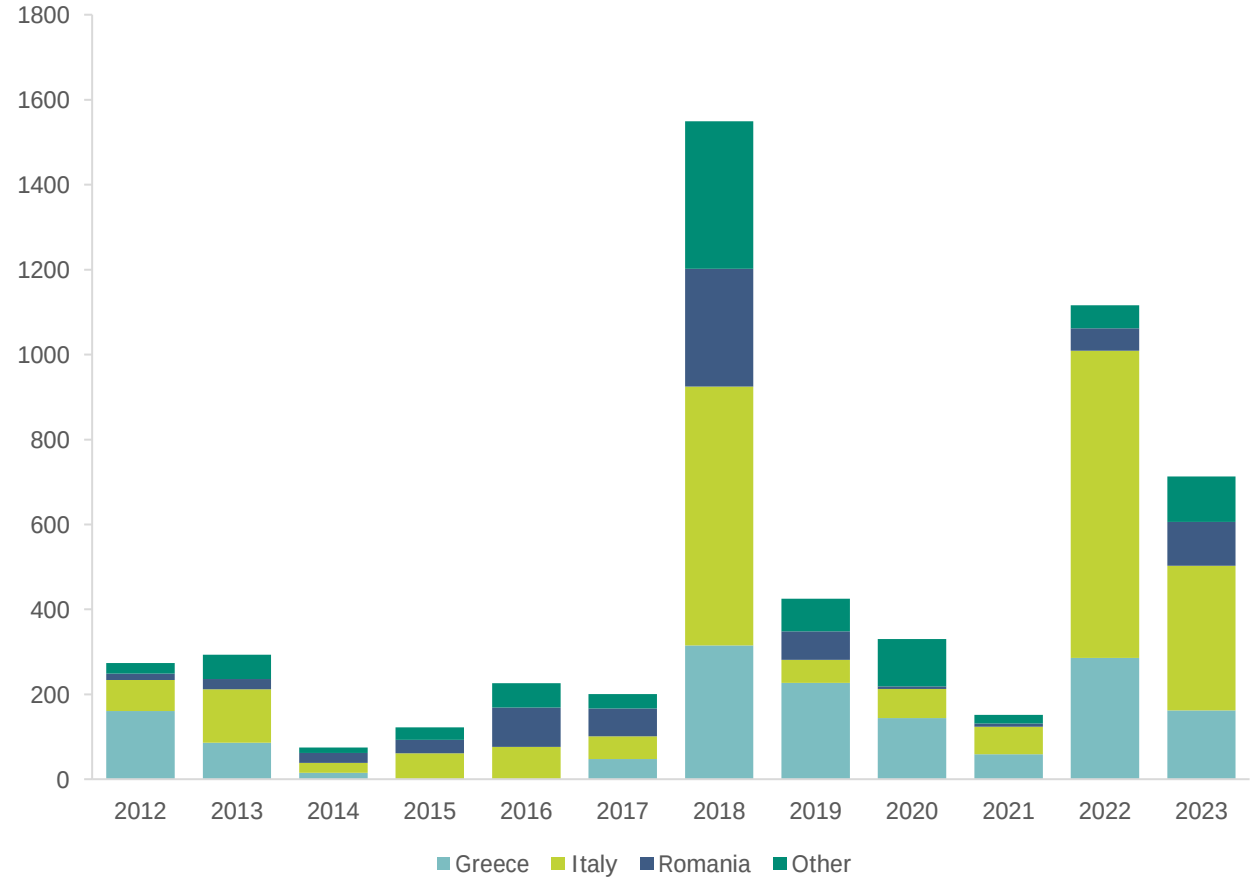
Source: International Air Travel Association and World Health Organisation

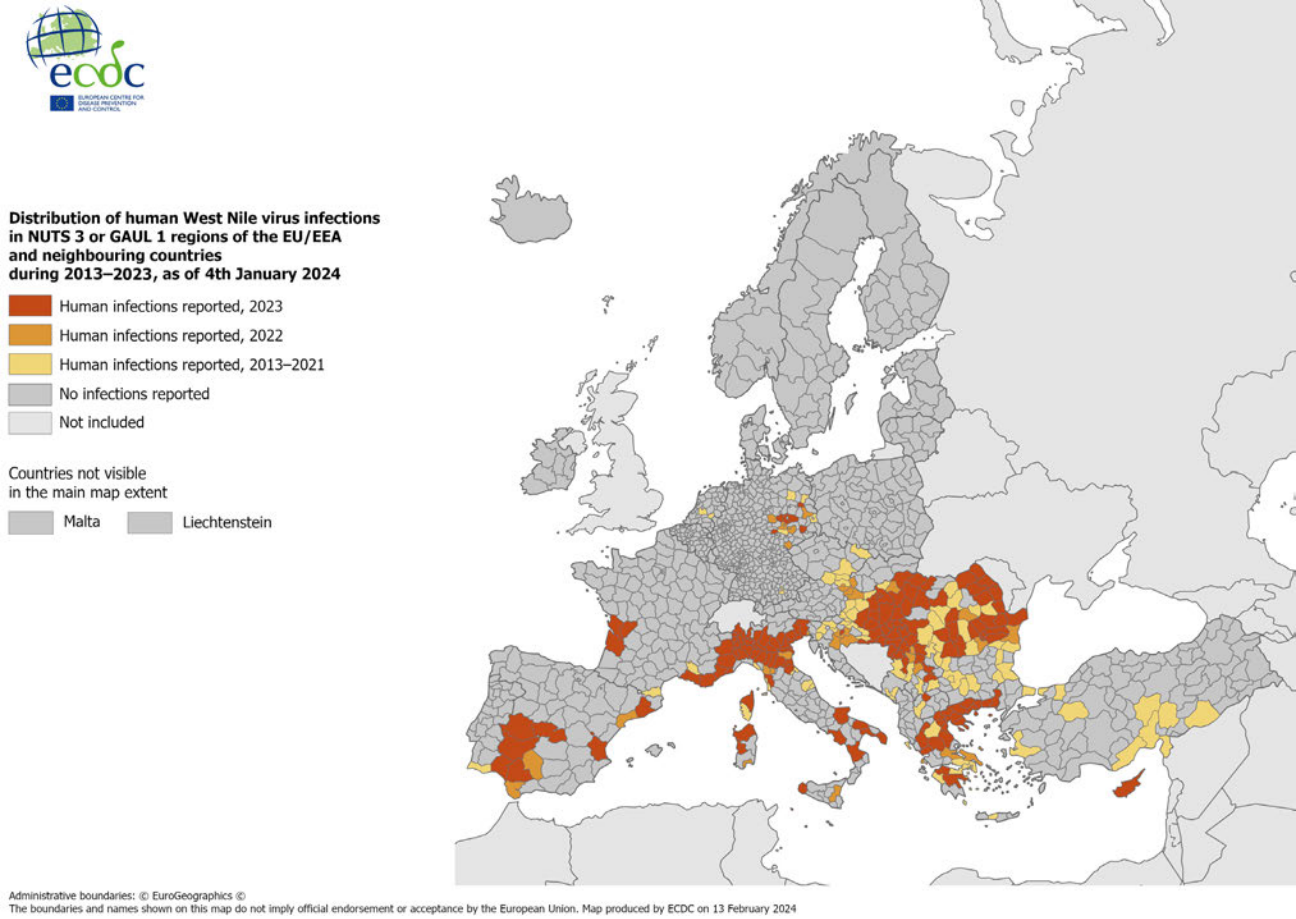
West Nile virus infections

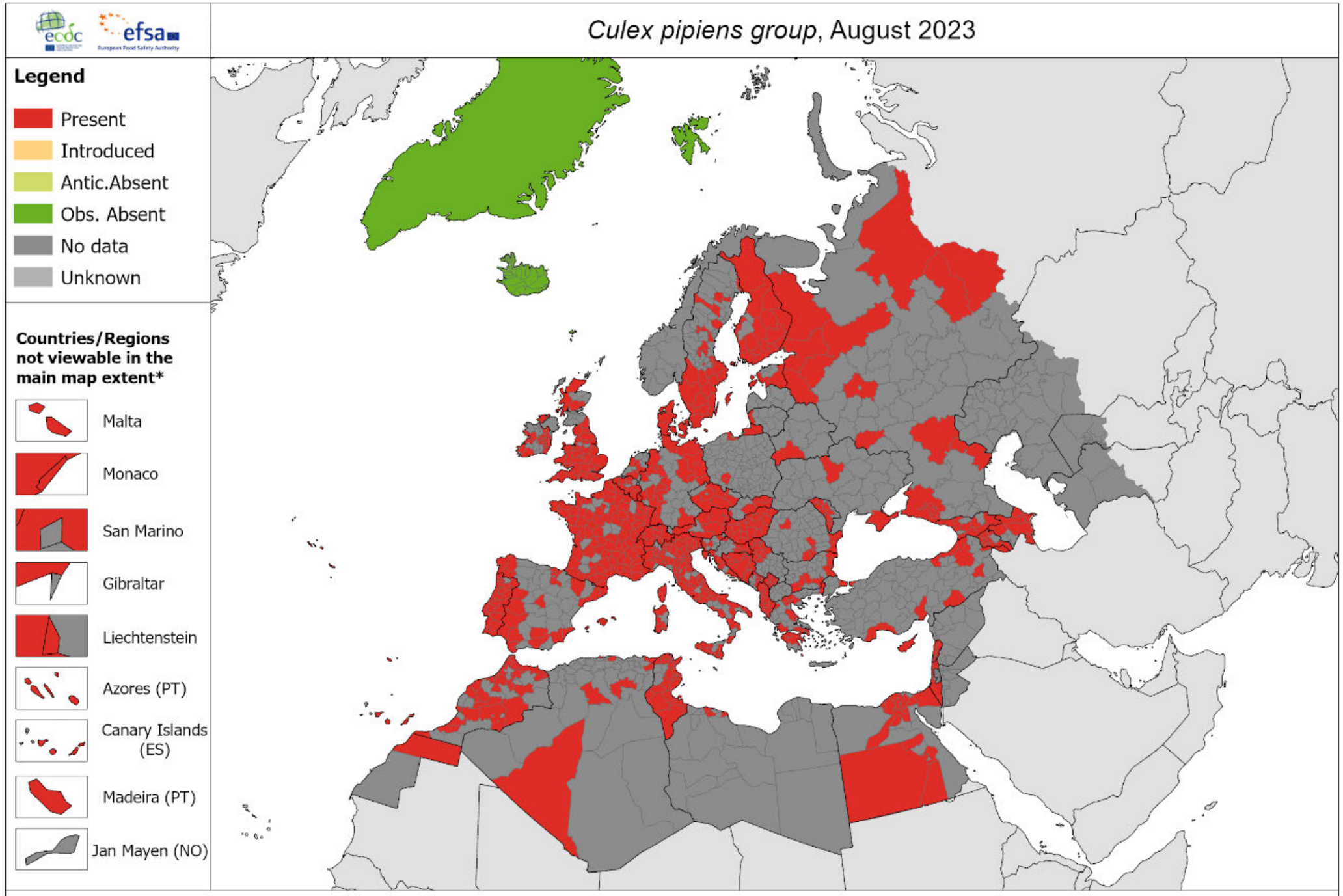
- Endemic to Europe
- Primarily transmitted by the mosquito *Culex pipiens* (common house mosquito)
- Virus circulate in the bird population; humans and equids are dead-end hosts
- 1/5 people infected with West Nile virus will get sick

- On average, 460 cases per year in Europe; 98% are locally-acquired

Number of locally acquired cases of human West Nile virus infection per reporting EU/EEA country, 2012-2023 (n=5,476)







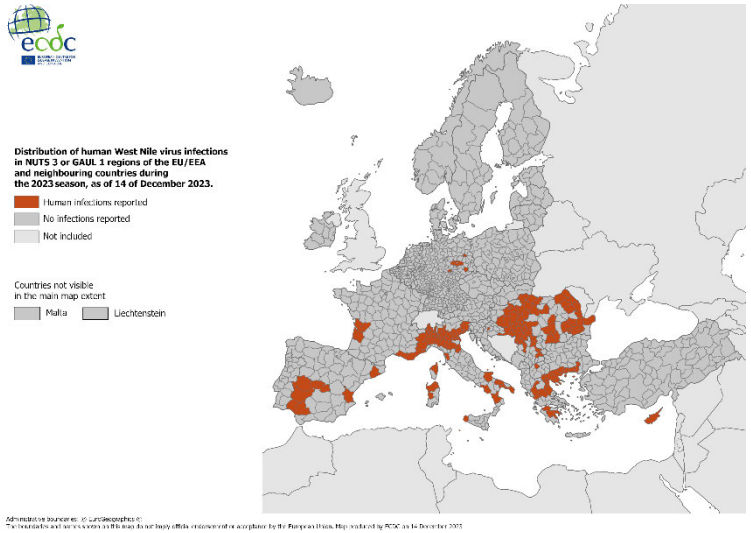
ECDC and EFSA, map produced on 25 Aug 2023. Data presented in this map are collected by the VectorNet project. Maps are validated by external experts prior to publication. Please note that the depicted data do not reflect the official views of the countries.
* Countries/Regions are displayed at different scales to facilitate their visualisation.The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union.Administrative boundaries © EuroGeographics, UNFAO.

Surveillance of West Nile virus infections

Enhanced surveillance from June to November, with weekly reports and monthly enhanced analysis

Weekly data collection on human cases,
through TESSy

Weekly updates on ECDC website, with a focus on distribution of human cases



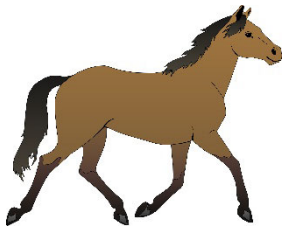
Timely inform SoHO authorities for implementation of **Commission Directive 2014/110/EU**, requesting that prospective blood donors are deferred for 28 days after leaving a risk area for locally acquired WNV infection, unless the result of an individual nucleic acid test is negative.

https://www.ecdc.europa.eu/en/west-nile-fever/surveillance-and-disease-data/disease-data-ecdc

Surveillance of West Nile virus infections

Weekly data collection on human cases, through TESSy

Collection of animal cases (equids and birds), through ADIS



<u>Monthly</u> enhanced analysis on ECDC website

Seasonal distribution

Human WNV infections | WNV outbreaks in equids and birds | Aggregated comparison

Figure 16.- Seasonal distribution of human west nile fever infections during the 2023 west nile fever transmission season and during the last 10 years.

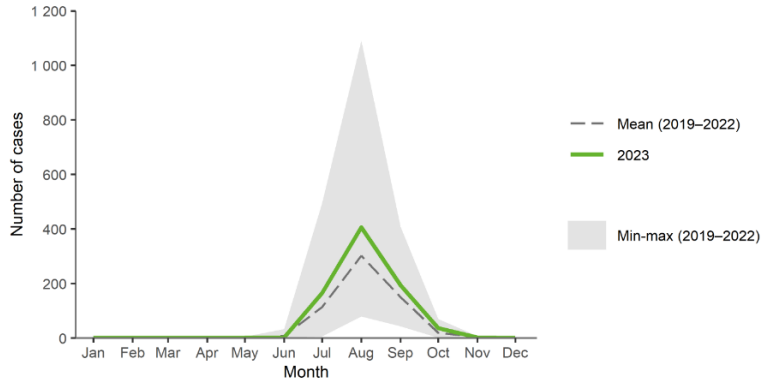


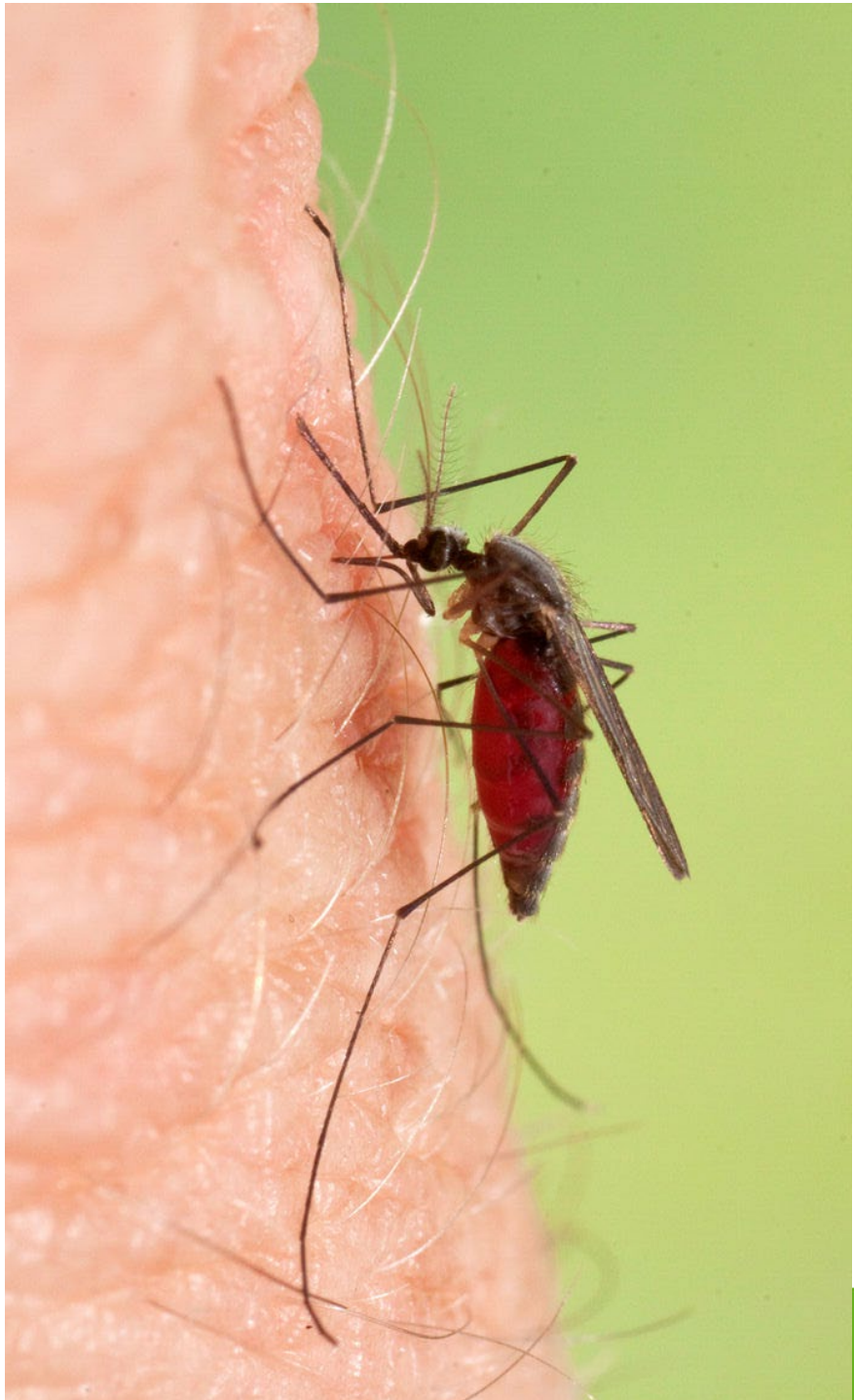
Figure 17.- Distribution of human west nile fever infections in NUTS3 or GAUL 1 regions of the EU/EEA and the EU neighbouring countries during the 2023 west nile fever transmission season and during the last 10 years.

Inform public health and veterinary authorities and provide a risk assessment of the situation

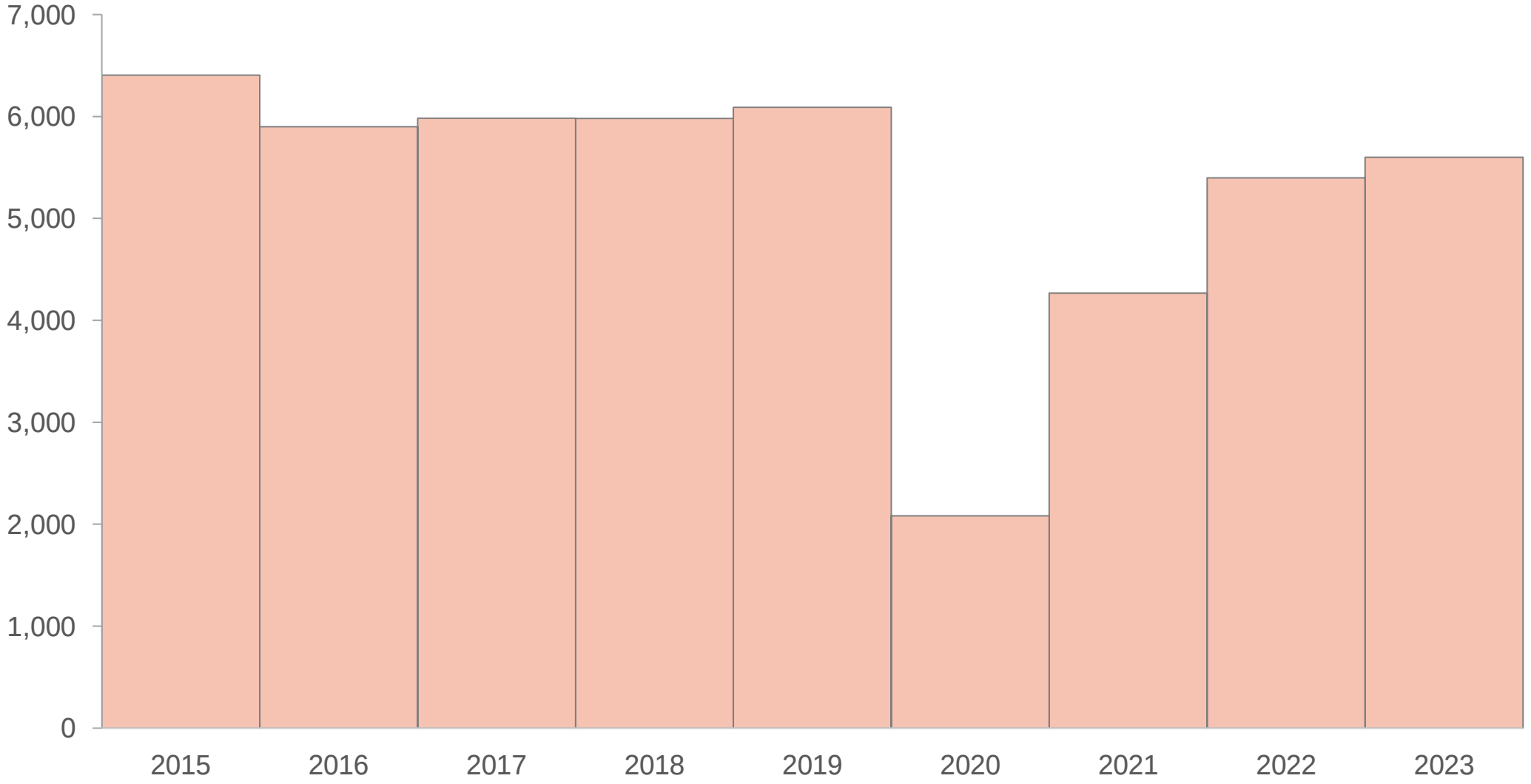
Situation in 2024, as of 12 June

Malaria

- Transmitted among humans by *Anopheles* mosquito
- The vast majority of people infected will develop symptoms
- On average, 5400 cases per year in Europe; >99% are imported.
- While autochthonous outbreaks are occurring within continental Europe, the disease is NOT considered endemic.

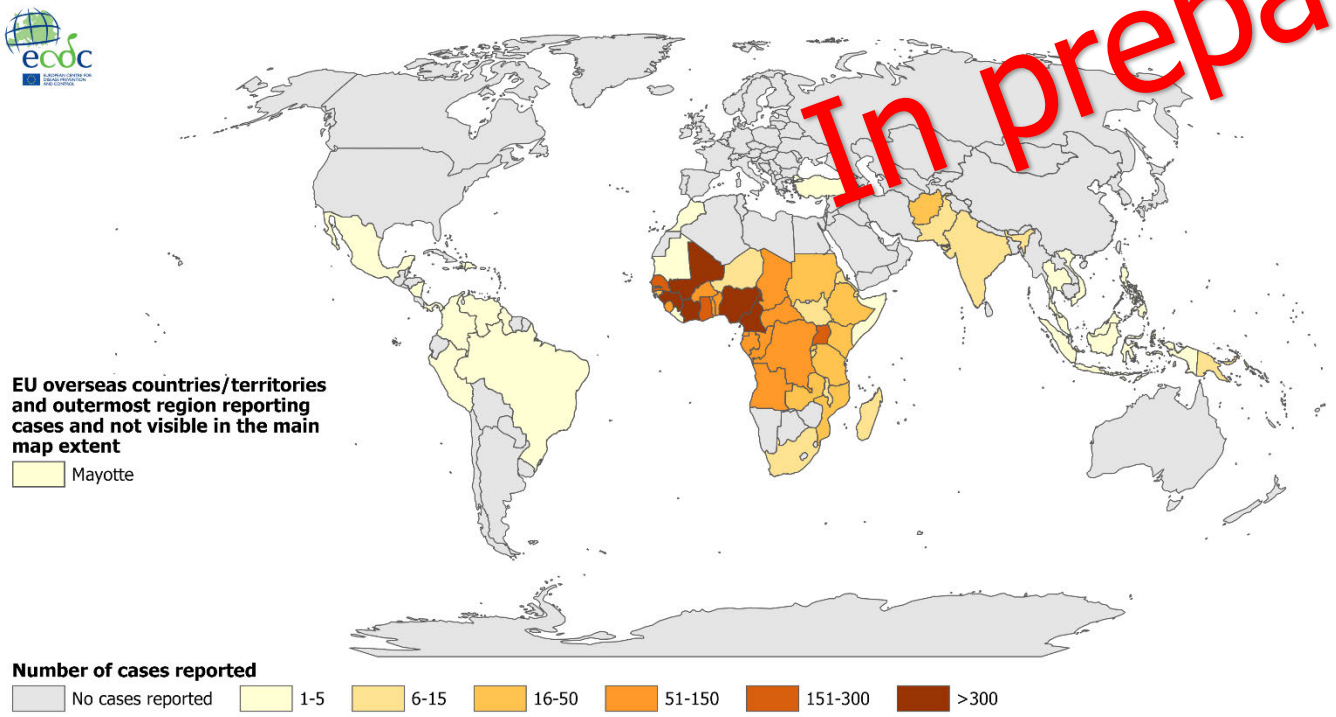


Travel-related cases of malaria reported in the EU/EEA, 2015-2023

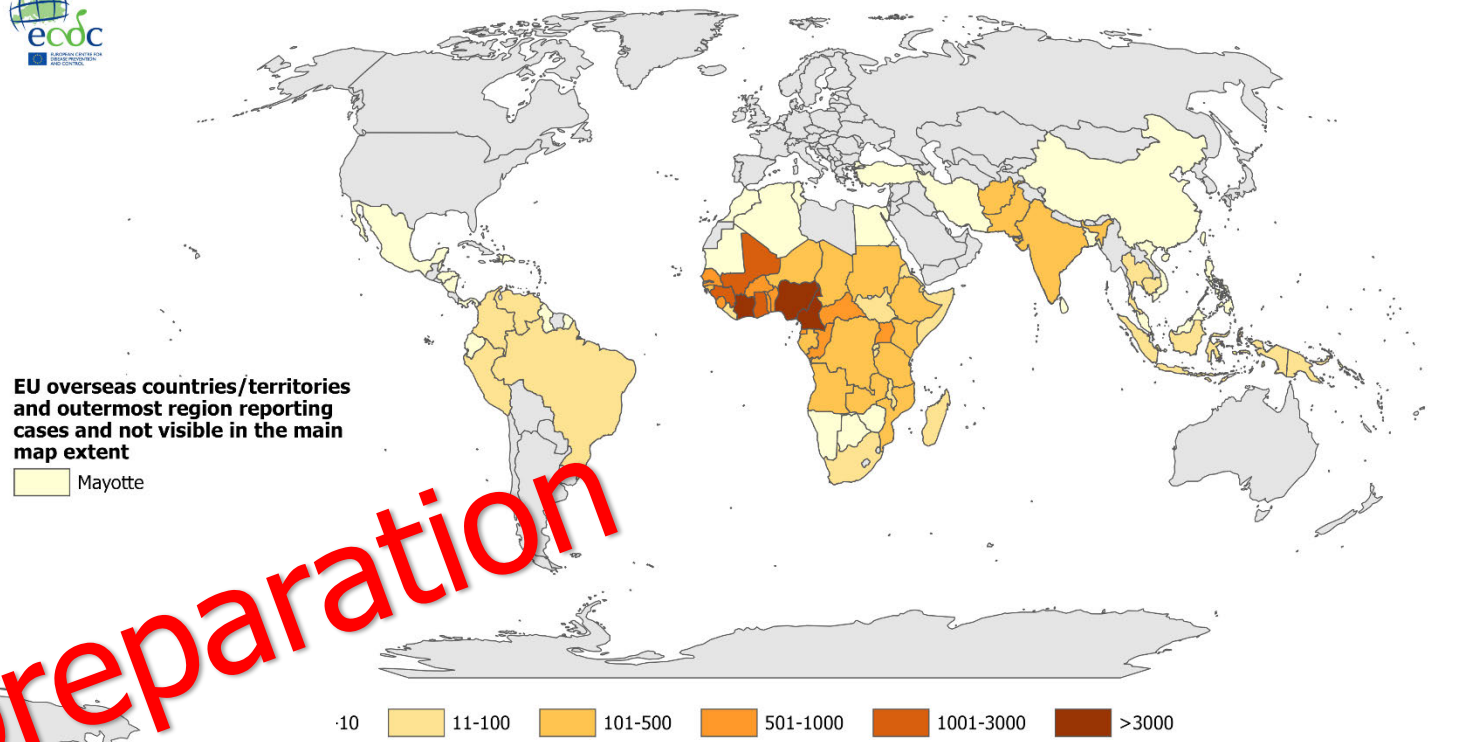


*preliminary data for 2023

Distribution of travel-associated malaria cases reported to ECDC, by place of infection, 2022



Administrative boundaries: © EuroGeographics ©UN-FAO. The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. Map produced by ECDC on 05 June 2024.



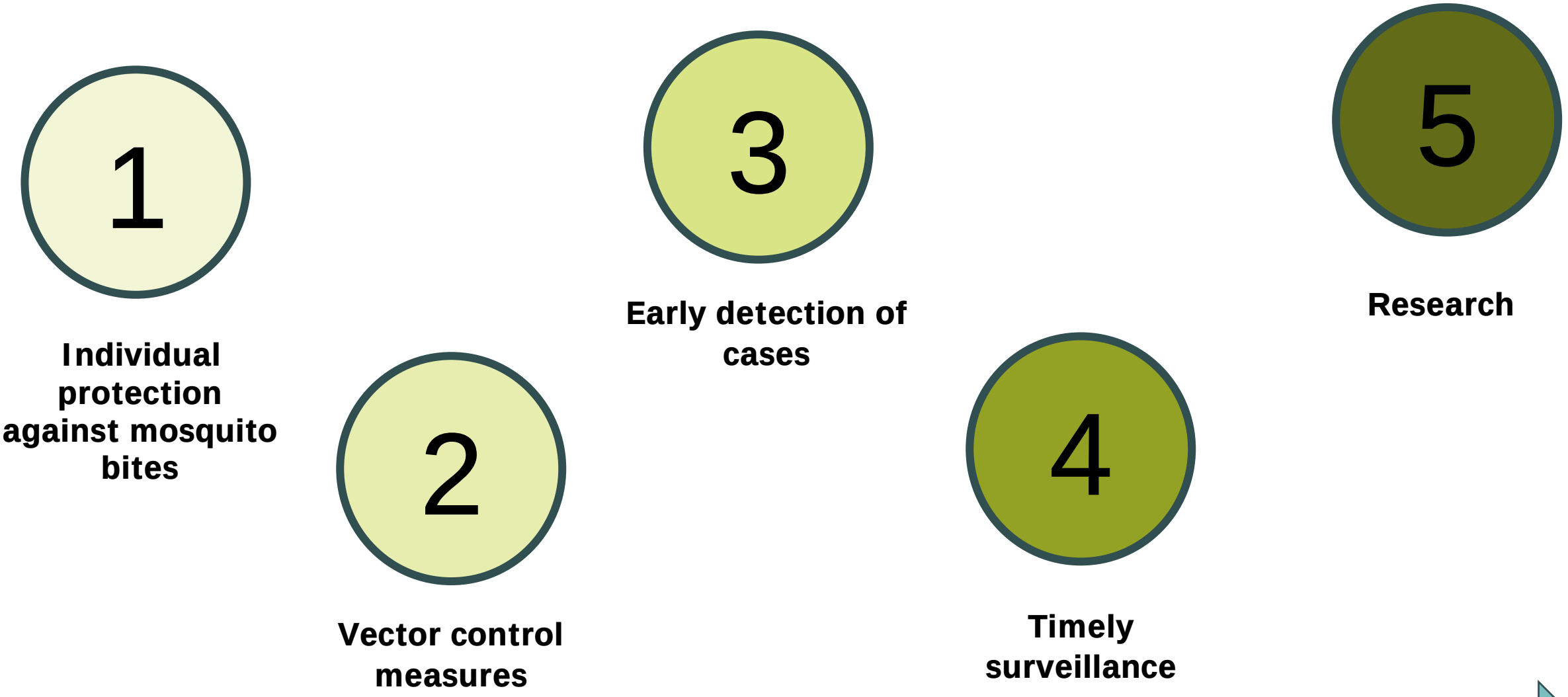
N-FAO. The boundaries and names shown on this map do not imply official endorsement or acceptance by the European Union. Map produced by ECDC on 05 June 2024.

ibution of travel-associated malaria cases reported to ECDC, by place of infection, 2018–2022

Locally-acquired cases of malaria

- 65 cases reported from 2015 to 2023, primarily by Greece (n=33).
- Among these, 43% are due to *Plasmodium vivax* and 52% are due to *P. falciparum*
- Cases are classified as introduced, health-care associated, airport/luggage malaria, laboratory acquired or cryptic.

Actions against mosquito-borne diseases



Thank you

Useful links

Autochthonous vectorial transmission of dengue virus in mainland EU/EEA, 2010-present: https://www.ecdc.europa.eu/en/all-topics-z/dengue/surveillance-and-disease-data/autochthonous-transmission-dengue-virus-eueea

Dengue worldwide overview: https://www.ecdc.europa.eu/en/dengue-monthly

Dengue imported cases: https://www.ecdc.europa.eu/en/dengue/surveillance/dengue-virus-infections-travellers

West Nile virus updates: https://www.ecdc.europa.eu/en/west-nile-fever/surveillance-and-disease-data/disease-data-ecdc

Annual Epidemiological Reports (AERs): https://www.ecdc.europa.eu/en/publications-data/monitoring/all-annual-epidemiological-reports

Mosquito surveillance maps: https://www.ecdc.europa.eu/en/disease-vectors/surveillance-and-disease-data/mosquito-maps

Surveillance_prevention_and_control_of_WNV_and_Usutu_virus_infections_in_the_EU-EEA: https://www.ecdc.europa.eu/sites/default/files/documents/Surveillance_prevention_and_control_of_WNV_and_Usutu_virus_infections_in_the_EU-EEA.pdf

A repository for guidance on emerging diseases and organ transplantation: proposal

SoHO-Net Organs Group meeting – 19 June 2024

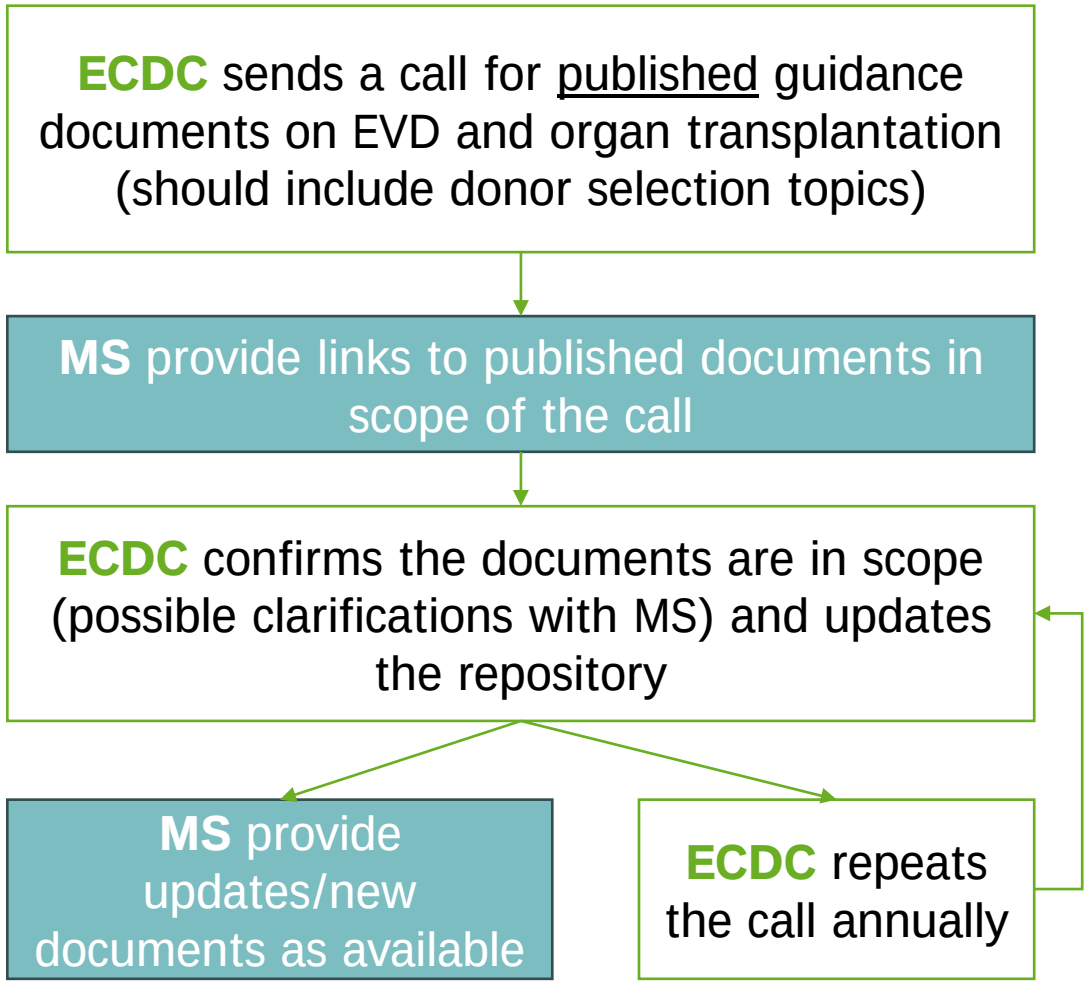
Aim

Within the **repository of policy and practice resources:**

Sharing of guidance documents published by Member States (MS) on the prevention of transmission of emerging and vector borne diseases (EVD) in organ transplantation

Rationale: Some affected MS are already addressing donor selection issues related to EVD while others are preparing for future cases in their country. All countries could benefit from the sharing of practices.

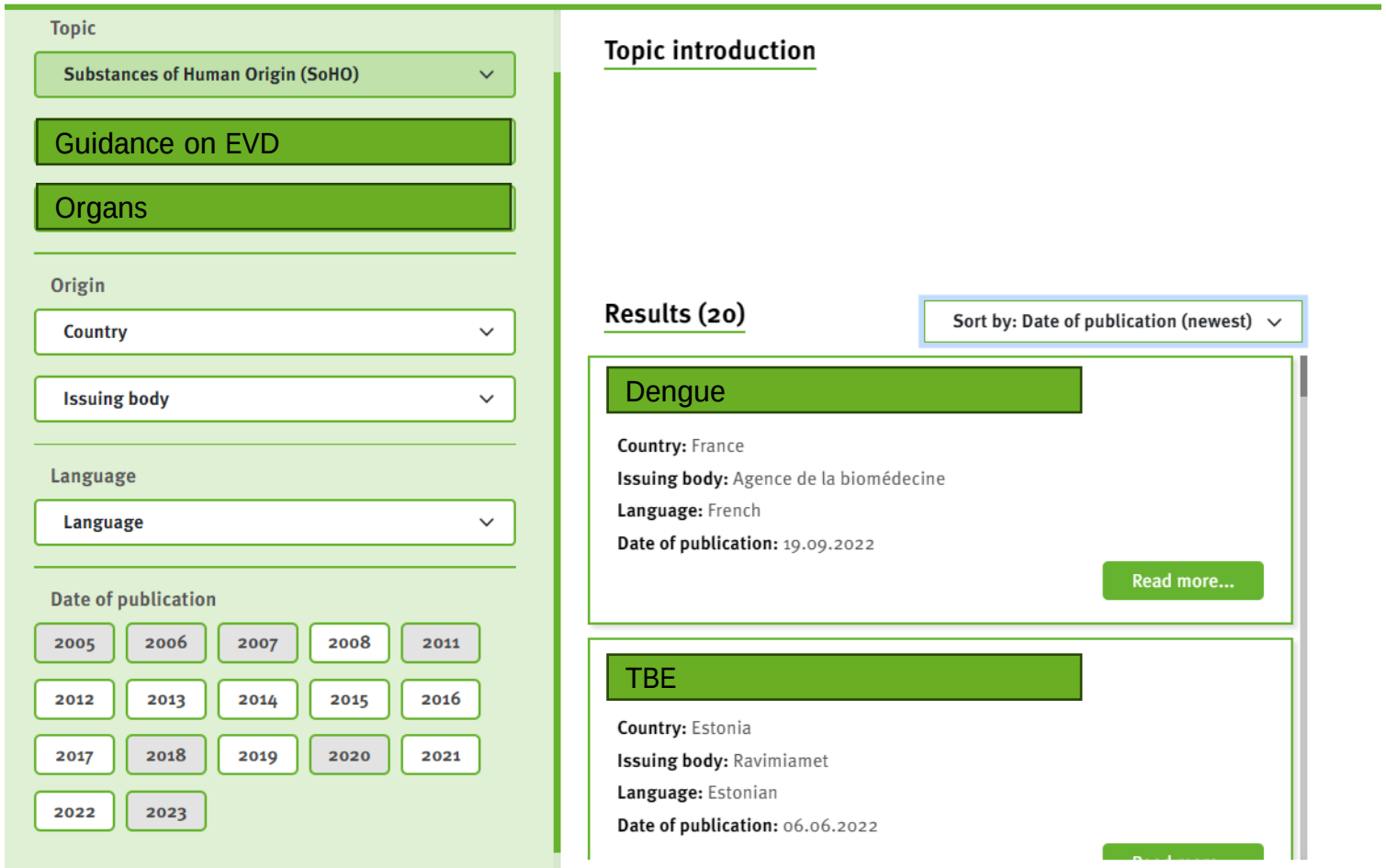
Methods and scope: for discussion



Scope:

- Published documents by national competent authorities or scientific societies (in EU/EEA)
- On emerging and vector-borne diseases: WNV infection, TBE, Dengue, Chikungunya, Zika…
- Includes (but not necessarily restricted to) guidance related to organ donor selection

Repository



Classification to be discussed

- A single group (“EVD”) as one guidance may cover several disease?
- Or disease related? “EVD guidance: WNV”
- Some guidance may cover several SoHO (tissues), these can be selected: a similar call will be discussed with other groups

Timelines

- Initial call for guidance: September – October 2024
- Confirmation of documents and update of the repository: November-December 2024
- Publication and annual call: January 2025+

Thank you

Session 9
Rapid risk assessments
19 June

Session overview

ECDC Rapid Risk Assessment (RRA) and technical reports

1. **BRAVEST Project status update** – Devy Mey and Luciano Potena, ESOT

2. **Presentation on ECDC rapid risk assessment (RRA) process and updates** – Orlando Cenciarelli, ECDC

3. **Discussion on the content of RRA for Organs** – All

4. **Request for NPFs as expert reviewers on ECDC RRA** – All

Luciano Potena
Devi Mey
ESOT

SOHO-NET ORGANS MEETING
18-19 JUNE 2024

EU4Health (2021-2027) – a vision for a healthier European Union

EU4Health is EU's response to COVID-19 to:

- *boost EU's preparedness for major cross border health threats by creating*
- *strengthen health systems so that they can face epidemics as well as long-term challenges*
- *make medicines and medical devices available and affordable, advocate the prudent and efficient use of antimicrobials as well as promote medical and pharmaceutical innovation and greener manufacturing*

BRAVEST

EU4Health Programme (EU4H)

Call for action grants under the Annual Work Programme 2021

Action grants on substances of human origin (SoHO) - increase resilience, ensure continuity of supply and access to safe and high quality therapies, in particular in times of crisis

This action aims to enable the medical/professional organisations and Member State authorities in SoHO subsectors to ***develop and exchange good practices for professionals and authorities to optimise supply and increase access to quality and safe use of critical therapies based on substances of human origin donated by fellow citizens.***

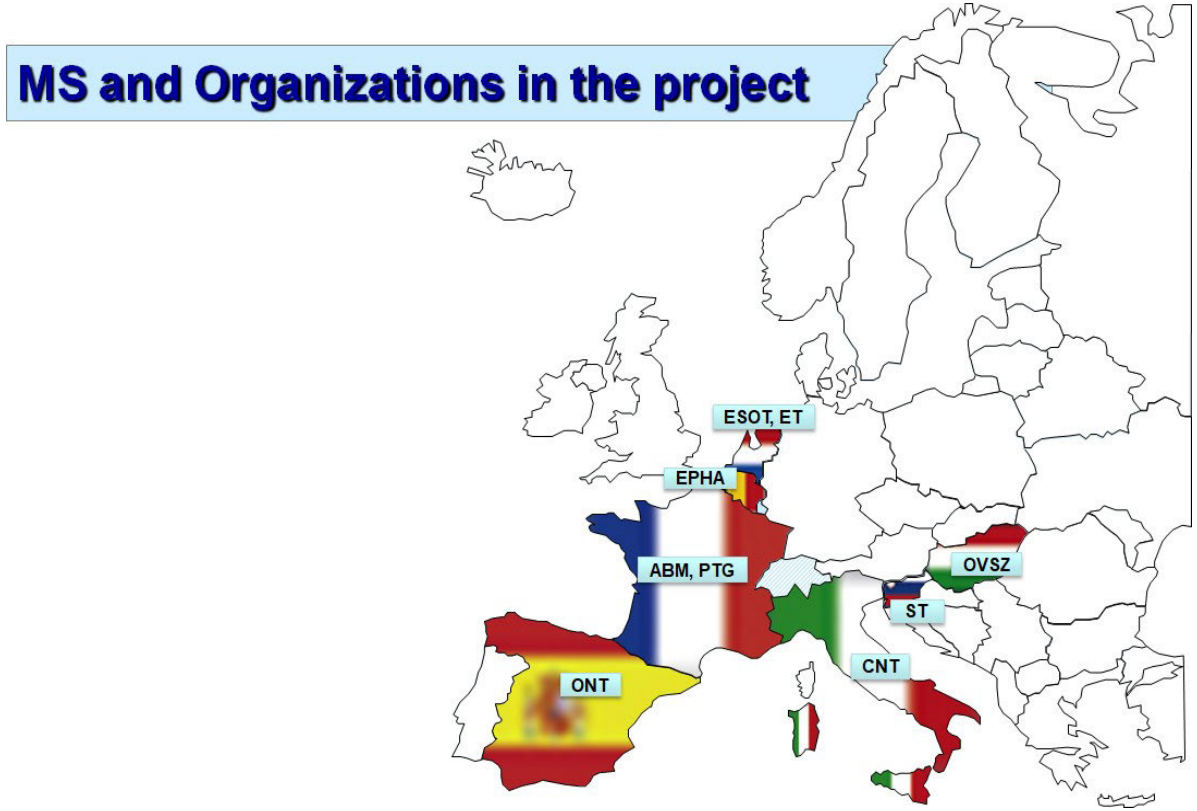
BRAVEST

Bravest project

Building **R**esilience **A**gainst crisis: a systematic and global approach to ad**V**anc**E** organ **S**afety and supply in **T**ransplantation

9 Partners

7 Countries



Aims

Analysing organizational and management procedures in organ donation and transplantation based on real world evidence and cutting-edge analysis methodologies.

- *Identify the most effective clinical practice and procedures during a crisis*
- *Propose sustainable innovative actions directed at improving the resilience of the donation and transplant networks*
- *Ensure the continuity of supply of organs while maintaining the safety of donation and transplant*
- *Increase the accessibility to transplantation for all patients with end-stage organ disease*

BRAVEST

BRAVEST project: three steps approach

1) Collect evidences and perform multiparametric analysis of the efficiency in pandemic management by the project partners
2) Development of specific recommendations in form of evidence-based guidelines
3) Analysis of the sustainability of the proposed measures

BRAVEST

Data analysis approach: study endpoints

Primary outcome measures

1. Change in rate per million inhabitants of deceased organ donors signalled and procured before, during and after the pandemic period

2. Change in number and kind of organs allocated and successfully transplanted before, during and after the pandemic period

3. Change in one year of patient and graft survival before, during, and after the pandemic period.

Secondary outcome measures, we will consider:

- Number of potential donors declined and the reason,

- Number of potential donors with a positive test for SARS-Cov2 and their outcome,

- Outcome of recipients receiving organs from SARS-Cov2 positive donors,

- Change in transplants from living donors (this outcome will be analysed only by aggregated data)

BRAVEST

Impact

Short term

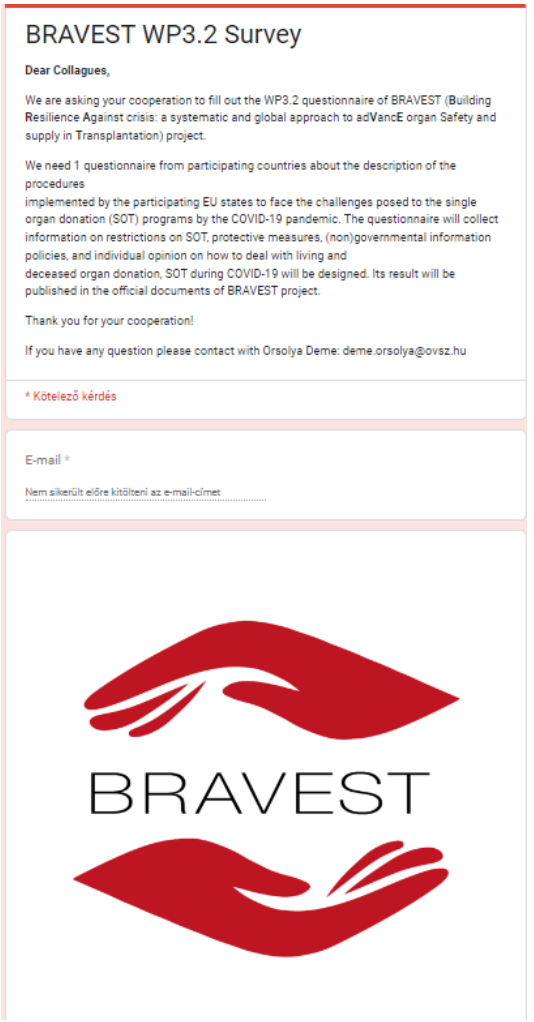
- Improve the knowledge on the effect of COVID-19 pandemic on donor procurement and transplant activities
- Develop evidence-based guidelines to improve resilience of donation and transplant systems (war, local crisis, migration, environmental etc.)

Long term

- Transferability of developed models to European Countries not included in the consortium, based on sustainability and cost-effectiveness analysis

BRAVEST

Step 1 – collection of country recommendations


BRAVEST WP3.2 Survey

Dear Collagues,

We are asking your cooperation to fill out the WP3.2 questionnaire of BRAVEST (Building Resilience Against crisis: a systematic and global approach to adVancE organ Safety and supply in Transplantation) project.

We need 1 questionnaire from participating countries about the description of the procedures
implemented by the participating EU states to face the challenges posed to the single organ donation (SOT) programs by the COVID-19 pandemic. The questionnaire will collect information on restrictions on SOT, protective measures, (non)governmental information policies, and individual opinion on how to deal with living and
deceased organ donation, SOT during COVID-19 will be designed. Its result will be published in the official documents of BRAVEST project.

Thank you for your cooperation!

If you have any question please contact with Orsolya Deme: deme.orsolya@ovsz.hu

* Kötelező kérdés

E-mail *

Nem sikerült előre kitölteni az e-mail-címet

BRAVEST

Survey consisting of 36 questions and its subquestions (132 items), based on the recommendations of the working group. We applied mixed method with opened and multiple choice questions.

Information on restrictions on SOT, protective measures, (non)governmental information policies, and individual opinion on how to deal with SOT during COVID-19 was designed.

Sections of the survey:

1. ***COVID-19 first outbreak in the country***
2. ***First measures***
3. ***Ongoing measures***
4. ***Measures regarding organization of international organ exchanges***
5. ***Measures regarding donors***
6. ***Measures regarding recipients***

BRAVEST

Descriptive analysis – Conclusions
COVID-19 first outbreak in the country

Were organ donation programs active during the first outbreak?

The donation programs during the first outbreak of COVID-19 experienced **varying degrees of restrictions** across different countries: options: open, closed, moderate, severe

Open Availability: Croatia, Slovenia, France, Belgium

Reasons: These countries maintained open availability for organ donation programs during the COVID-19 pandemic, **indicating a proactive approach to ensuring continued access to transplantation services without significant restrictions.**

Moderate Limitations: Italy, The Netherlands, Hungary, Germany

Reasons: These countries implemented moderate restrictions on organ donation programs, which included **temporary suspensions of specific programs** (e.g., Living Transplantation program in Italy, lung donation program in Hungary), **restrictions due to resource constraints** (e.g., lack of intensive care beds in The Netherlands), and **enhanced donor evaluation procedures** (e.g., PCR testing, careful assessment of infection signs in Germany).

Severe Limitations: Spain

Reasons: Spain experienced severe limitations on organ donation programs during the most critical weeks of the first wave of the pandemic. The **collapse of the healthcare system and overwhelmed ICU capacity** necessitated prioritization of resources, leading to substantial decreases in donation activity. **Organ donation was limited to optimal donors, and uncontrolled DCD programs were closed. Additionally, donors who tested positive for COVID-19 or exhibited symptoms suspicious of COVID-19 were rejected.**

Descriptive analysis – Conclusions
COVID-19 first outbreak in the country

Were transplantation programs active during the first outbreak?

The transplantation programs during the first outbreak of COVID-19 experienced **varying degrees of restrictions** across different countries: options: open, closed, moderate, severe

Severe Limitations in Spain, Hungary

Reasons: Collapse of the healthcare system, **overwhelmed ICU capacity**, priority given to urgent cases and critically ill individuals, substantial decrease in transplantation activity, **live donor transplant programs were closed**.

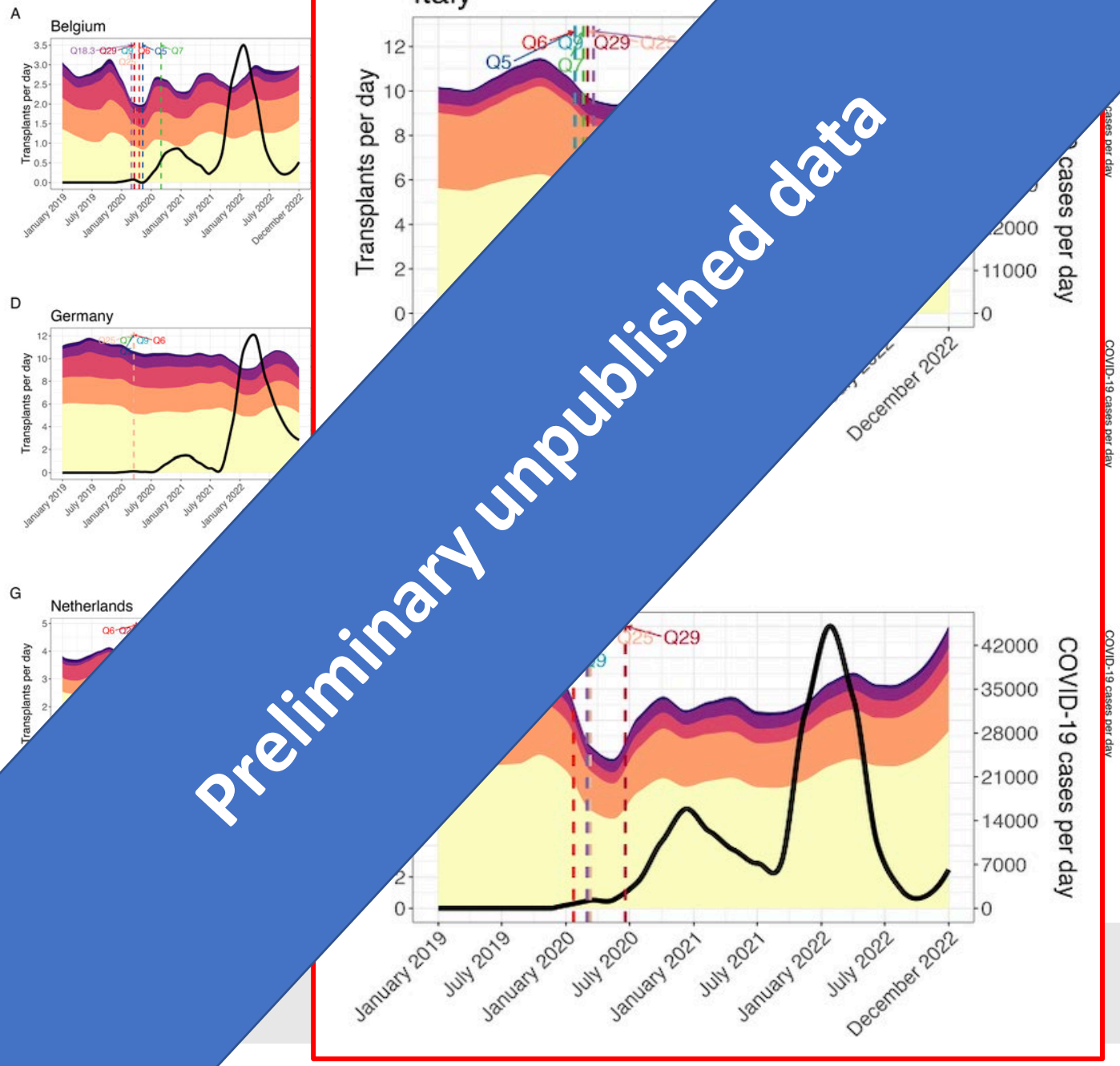
Moderate Restrictions in Italy, The Netherlands, Germany, France, Belgium

Reasons**: Temporary suspension of living donor transplantation program**, **closure of some transplantation programs**, prioritization of resources, variations in transplantation decisions among centers based on **individual risk-benefit evaluations**, **suspension of specific types of transplants** (e.g., renal transplantation in France temporarly suspended).

Limited Restrictions/Open Programs in Slovenia

Reasons: Transplantation programs remained open and active without significant restrictions during the first outbreak, indicating a **proactive approach** to maintaining transplantation services during the pandemic.

BRAVEST



Q5. Adoption of 1st measure regarding organ donation at national level

Q6. Adoption of 1st measure regarding transplantation activity

Q7. Adoption of 1st measure regarding transplant waiting list

Q9. 1st COVID-19 specific OD&T recommendation or guideline issued

Q18.3. First wave's peak of the COVID-19 pandemic

Q25. Initiation of SARS-CoV-2 PCR (NAT) screening of deceased donors

Q29. Initiation of the SARS-CoV-2 PCR/NAT screening of recipients

BRAVEST

Next steps and challenges

Full completion of survey analysis for publication

Completion of GDPR implementation to comply with the different interpretations across countries which currently represent a barrier to clinical data collection

- Development of project specific DPIA and DSA with partners

Collection of clinical data from data controllers and processor(s)

BRAVEST

BRAVEST: **B**uilding **R**esilience **A**gainst crisis: a systematic and global approach to ad**V**anc**E** organ **S**afety and supply in **T**ransplantation

Funded by the European Union

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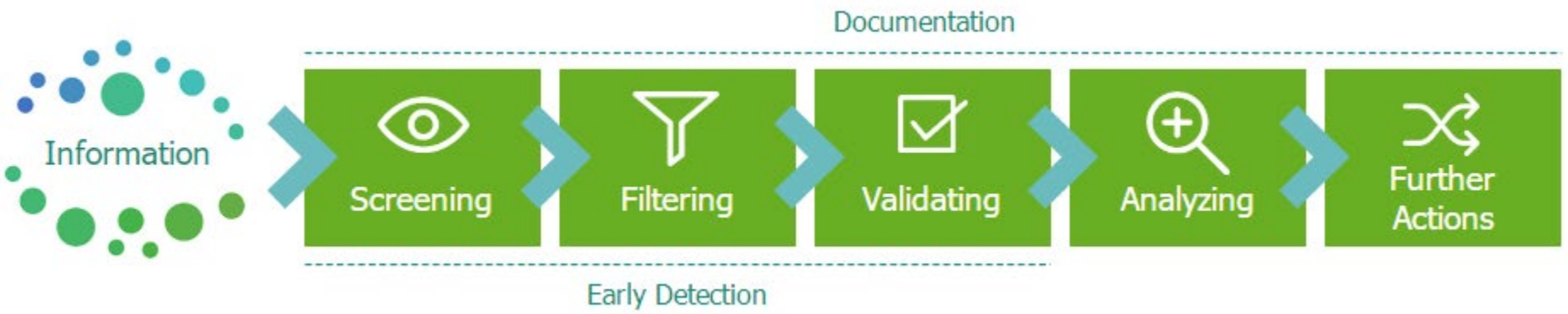
REF: 101056986 — BRAVEST — EU4H-2021-PJ

ECDC rapid risk assessment (RRA) process and updates

Orlando Cenciarelli, Emergency Preparedness and Response, ECDC

SoHO-Net meeting, Stockholm, 19 June 2024

ECDC threat detection: the epidemic intelligence process



Review of large number of items

Selection of relevant items

Use official sources to validate information

Contextualize information for assessment

Rapid sharing of information.
Reporting at Round Table.
Rapid Risk Assessment.

Threat detection – sources and validation

Indicator-based surveillance

TESSy
(EpiPulse cases)
Web scraping

Event-based surveillance

Restricted platforms:
- EpiPulse Events
- EWRS
- WHO Event Information site
- RASFF

Official public sources:
- National public health institute websites
- WHO websites
- CDC websites

Media monitoring (including social media)

Epidemic Intelligence from Open Sources (EIOS)

Social media platforms

Other web aggregators as backup

Global coverage

- In EU/EEA:
  - ECDC disease specific networks
  - Epidemic Intelligence activities
- Outside EU/EEA:
  - Public Health Institutes/Ministries of health where direct links (e.g. existing MoU, personal contacts)
  - Other CDCs – e.g. Africa CDC
  - World Health Organization (mainly WHO/Europe)

Outputs

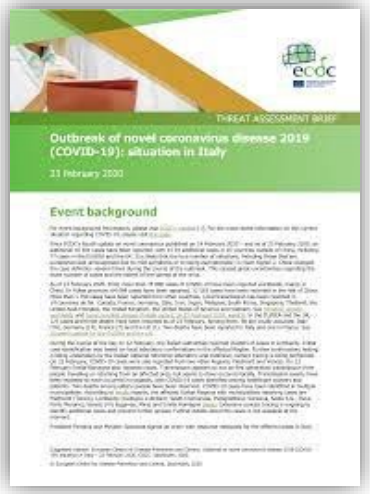
Communicable disease threat reports

Restricted and Public versions
Daily and weekly editions

Risk assessment outputs

Epidemiological Updates

Threat Assessment Brief



Rapid Risk Assessment

What is an ECDC risk assessment?

Assessment in EU: relative quantification of the risk to human health of an event (potential threat) represents in one or more EU/EEA countries or for EU/EEA citizens living in affected areas outside of the EU.

- **Support** the EU/EEA countries public health authorities and the EC in their preparedness and response to the threat by:
  - **Alerting** about the event
  - Providing **timely information** on the estimated risk related to the public health threat
  - Addressing **uncertainty** by using a **systematic appraisal** of the best scientific evidence available
  - Determining whether a **response** is needed
  - Providing [non-binding] **recommendations** for mitigating the risks

- **Inform** health professionals and the public at large (e.g. clinicians, media, travellers...)

Triggering criteria for ECDC rapid risk assessments

- Outbreak extending to more than one EU/EEA country
- Risk of introduction to and/or propagation within the EU/EEA
- Event for which cross border contact tracing is needed
- Unusual or unexpected event
- Outbreak of unknown origin
- Emerging disease(s) affecting touristic areas
- Contaminated food product(s) with EU dimension

- Event triggering high media attention

ECDC process for conducting a RRA

Decision to develop an RRA

Multidisciplinary **internal response team**

Notification to ECDC external stakeholders
- Advisory Forum members
- National Coordinators (Coordinating Competent Body)
- NFP for Preparedness and Response; for Threat Detection, EWRS and IHR; for specific area/disease
- European Commission

Independent external rapid review

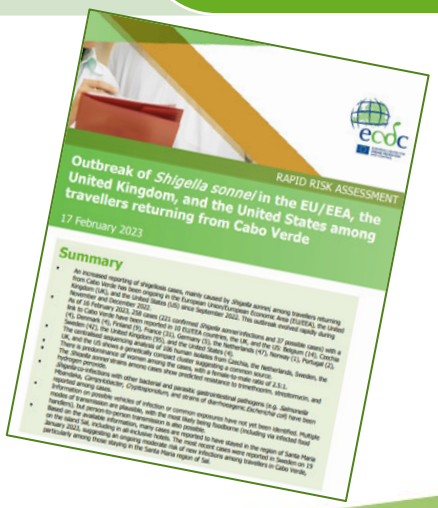
External distribution under embargo:
- Advisory Forum members
- National Coordinators (Coordinating Competent Body)
- NFP for Preparedness and Response; for Threat Detection, EWRS and IHR; for specific area/disease
- European Commission

Publication ECDC

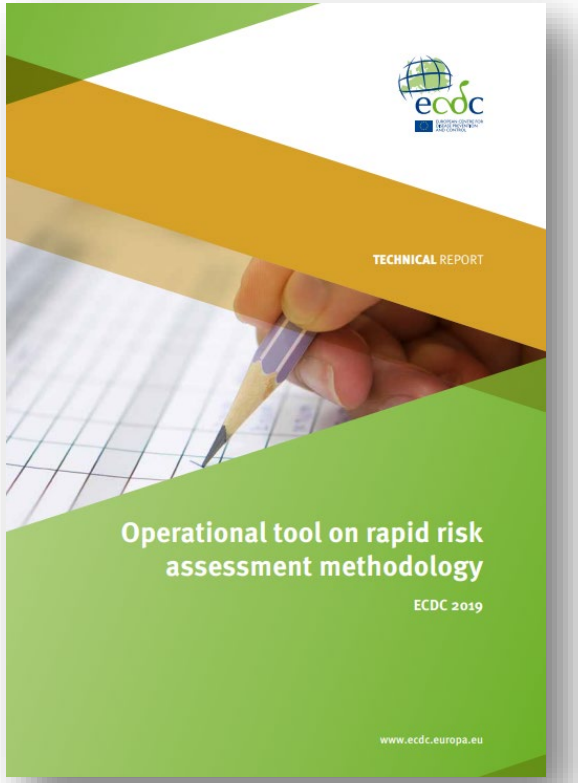
EC posts on EWRS

MS can post on national websites

Ensuring traceability and transparency:
- Rapid risk assessments are registered and followed in the ECDC Scientific Advice Repository and Management System.
- Declarations of interest are collected and assessed for all external reviewers prior to review and publication.
- Actions taken (or not taken) on external reviewers' and AF comments and edits are stored.



ECDC operational tool on rapid risk assessment methodology



Aim

- Support for consistency, reproducibility and transparency using a systematic approach
- Provide an analytical framework
- Helps to manage time constraints limited evidence available expert opinions

Ongoing, 2024

- Review and update of methodology. Maintain the basis, with further improvement of the existing algorithm.

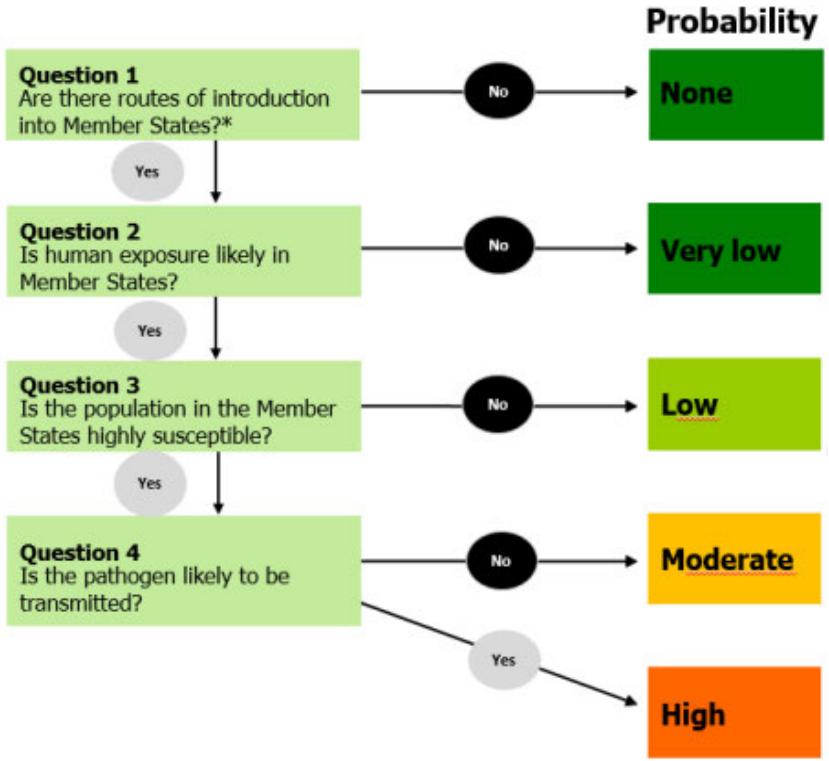
ECDC's amended mandate, Article 8a:

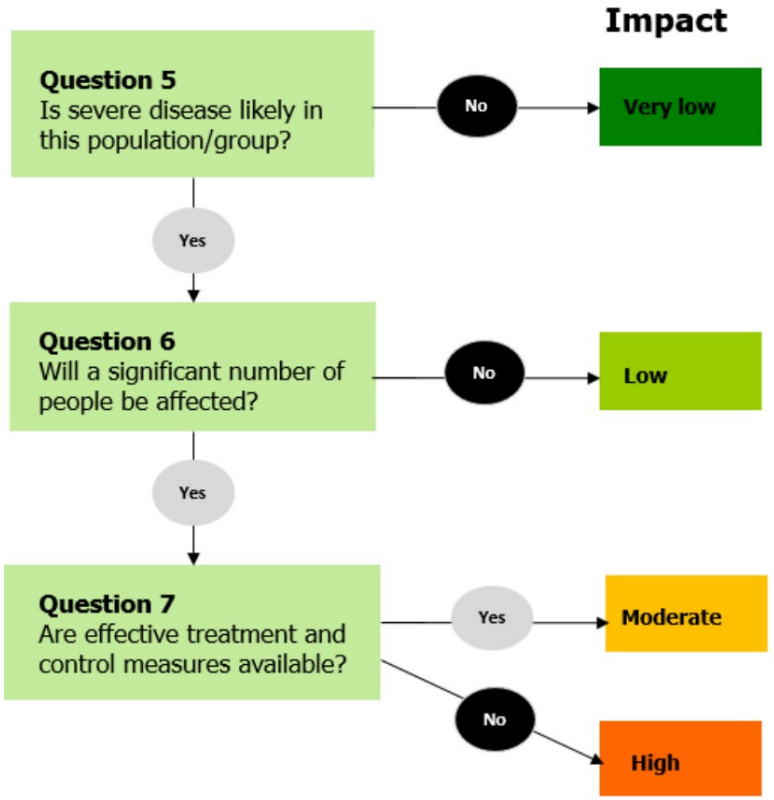
- "*Risk assessments…**shall include general and targeted*** **(non-binding)** ***science-based recommendations and options for response as a basis for coordination in the HSC***".

https://www.ecdc.europa.eu/sites/default/files/documents/operational-tool-rapid-risk-assessment-methodolgy-ecdc-2019.pdf

Assessing the risk /1

Risk = Probability X Impact





https://www.ecdc.europa.eu/sites/default/files/documents/operational-tool-rapid-risk-assessment-methodolgy-ecdc-2019.pdf

Assessing the risk /2

Impact \ Probability	None	Very low	Low	Moderate	High
Very low	None	Very low risk	Low risk	Low risk	Moderate risk
Low	None	Low risk	Low risk	Moderate risk	Moderate risk
Moderate	None	Low risk	Moderate risk	Moderate risk	High risk
High	None	Moderate risk	Moderate risk	High risk	Very high risk

Key steps for the development of a RRA

1. Signal verification and event information systematically collected
2. RRA decision: at the ECDC RT meeting
3. Internal Response Team: formulate the risk question(s) and develop text
4. Conduct a rapid but structured literature review
5. Appraise the evidence and acknowledge confidence, unknowns & limitations
6. Estimate and assess the risk using the operational algorithms
7. Integrate uncertainties and limitations
8. Provide recommendations for member state public health authorities
9. Prepare RRA communication material
10. Re-assess new information and decide on need to update RRA

ECDC Rapid Risk Assessment - structure

RAPID RISK ASSESSMENT

Outbreak of *Shigella sonnei* in the EU/EEA, the United Kingdom, and the United States among travellers returning from Cabo Verde

17 February 2023

Summary

- An increased reporting of shigellosis cases, mainly caused by *Shigella sonnei* from Cabo Verde has been ongoing in the European Union/European Economic Area (EU/EEA), the United Kingdom (UK), and the United States (US) since September 2022. This outbreak...
- As of 16 February 2023, 258 cases (221 confirmed *Shigella sonnei* infections with link to Cabo Verde have been reported in 10 EU/EEA countries, the UK, and the US: Belgium (4), Denmark (4), Finland (9), France (31), Germany (5), the Netherlands (4), Sweden (42), the United Kingdom (95), and the United States (4).
- The centralised sequencing analysis of 106 human isolates from Czechia, the UK, and the US shows a genetically compact cluster suggesting a common source.
- There is predominance of women among the cases, with a female-to-male ratio...
- The *Shigella sonnei* strains among cases show predicted resistance to trimethoprim, hydrogen peroxide.
- *Shigella* co-infections with other bacterial and parasitic gastrointestinal pathogens (Mbandaka, *Campylobacter*, *Cryptosporidium*, and strains of diarrhoeagenic *E.* reported among cases.
- Information on possible vehicles of infection or common exposures have not... modes of transmission are plausible, with the most likely being foodborne (... handlers), but person-to-person transmission is also possible.
- Based on the available information, many cases are reported to have stayed on the island Sal, including in all-inclusive hotels. The most recent cases were... January 2023, suggesting an ongoing moderate risk of new infections among... particularly among those staying in the Santa Maria region of Sal.

RAPID RISK ASSESSMENT

Increase of pertussis cases in the EU/EEA

8 May 2024

Summary

Epidemiological situation

Pertussis is an endemic disease in the EU/EEA and worldwide. Every three to five years, larger epidemics are expected even with high vaccination coverge.

After a few years of limited circulation in the EU/EEA, particularly during the COVID-19 pandemic, more than 25 000 cases of pertussis were reported in 2023, and more than 32 000 between January and March 2024. Similar numbers were observed in 2016 (41 026) and 2019 (34 468).

During 2023-24, in 17 EU/EEA countries, infants (those under the age of one year) represented the group with the highest reported incidence, whereas in six countries, the highest incidence is reported in adolescents 10-19 years. The majority of deaths occurred in infants. These surveillance data need to be interpreted with caution due to known differences in Member State surveillance systems, availability of laboratory methods, testing practices, as well as vaccination schedules. Furthermore, case ascertainment can vary by age group. In many countries, maternal vaccination programmes are used to protect infants in the first months of life. However coverage data, where available for such programmes, appears to be sub-optimal.

The observed epidemiological picture can be ascribed to a number of factors, which include: expected epidemic peaks, presence of unvaccinated or not up to date vaccinated individuals, waning immunity, decreased contribution of natural boosting in the overall population during the COVID-19 pandemic period.

Risk assessment

The risk from pertussis was assessed for four different population groups as a product of the probability of infection and its impact. The overall risk is assessed as **high** for unimmunised or partially immunised **infants <6 months of age**, as they represent the group with the highest morbidity and mortality from pertussis.

Infants >6 months and children up to 15 years of age have a **moderate** risk if they are unimmunised or partially immunised and have a low risk if they are fully vaccinated according to national immunisation schedules.

Older adolescents >16 years and adults up to 64 years of age have a **moderate** risk which is reduced to low if they have recently received a booster dose.

Finally, **older adults (≥65 years of age) and persons of any age with underlying conditions** such as asthma, chronic obstructive pulmonary disease (COPD) or immunosuppression, have an overall **moderate** risk from pertussis, having a moderate probability of infection and moderate impact (i.e. a higher probability of experiencing severe illness than individuals in the younger age/group).

Suggested citation: European Centre for Disease Prevention and Control. Increase of pertussis cases in the EU/EEA, 8 May 2024. Stockholm: ECDC; 2024.

Catalogue number: TQ-02-24-500-EN-N, ISBN: 978-92-9498-717-4, DOI: 10.2900/831122

- Title
- Summary
- Epidemiological situation (brief description of the current event)
- Risk question(s)

Risk assessment for the EU/EEA

ECDC recommendations for mitigating the assessed risks

Limitations

References

Technical Annex (can include event background and/or disease background and other in-depth information related to the RRA)

SoHO aspects in the ECDC rapid risk assessment

Consideration/non-binding recommendation for public health and SoHO authorities

THREAT ASSESSMENT BRIEF

Risks posed by reported increased circulation of human parvovirus B19 in the EU/EEA

5 June 2024

Summary

ECDC is following reports from several European Union and European Economic Area (EU/EEA) countries of substantial increases in the detection of parvovirus B19 (B19V). This Threat Assessment Brief has been developed to raise awareness among public health and substances of human origin (SoHO) professionals and competent authorities about this event, particularly as regards population groups at high risk for severe complications, and suggest actions that can be taken to address this situation.

Epidemiological situation

Since March 2024, nine EU/EEA countries have reported increased detections of B19V on the European surveillance portal for infectious diseases, EpiPulse, from a number of monitoring systems, mostly during late 2023 and early 2024. As a response to an inquiry from ECDC to the National Focal Points (NFPs) in the ECDC-SoHO network blood group [1] on B19V infections, 10 countries reported an increase in reactive tests for B19V in blood donors or in donations of plasma for fractionation during the first months of 2024 compared to the same period in 2023.

Risk assessment

Based on the unusually high numbers of B19V cases reported in 14 EU/EEA countries, the risk of infection is assessed in four population groups as follows:

- **The risk for the general population** is assessed as **low**, as most infections are in the form of a mild exanthematous disease of childhood, although some complications may occur.
- **The risk for pregnant women**, less than 20 weeks gestation is assessed as **low to moderate**, considering the uncertainties about the virus circulation, the fact that an estimated 30–40% of women of childbearing age are susceptible to the infection, and severe outcomes occur in a small percent of infected pregnancies.
- **The risk for immunosuppressed people** is assessed as **moderate**, as these patients cannot clear the infection and can suffer chronic anaemia, pancytopenia, graft loss or dysfunction and organ-invasive disease.
- **The risk for people with chronic haematological diseases** (e.g. sickle cell disease, thalassaemia, etc.) is assessed as **moderate**, as B19V infection can cause transient aplastic crisis.

Recommendations

For public health authorities

ECDC recommends that public health authorities in the countries should:

- **Raise awareness among clinicians** of the observed increase of B19V to assist in counselling and managing their patients appropriately.
- **Conduct risk communication to the risk groups**, including pregnant women, immunosuppressed and transplant recipients, and patients with chronic blood disorders, particularly haemolytic anaemias.

Suggested citation: European Centre for Disease Prevention and Control Risks posed by reported increased circulation of human parvovirus B19 in the EU/EEA – 5 June 2024. ECDC: Stockholm; 2024.

ISBN 978-92-9498-725-9; doi: 10.2900/453481; Catalogue number TQ-02-24-605-EN-N

ECDC considerations for public health and SoHO authorities

For SoHO professionals and competent authorities

Transmission of B19V through SoHO has been described in the literature via transfusion of red blood cells and platelets, treatment with plasma-derived medicinal products [17-22], and hematopoietic stem cells (HSC) [23] and solid organ transplantation [24]. However, clinically significant transfusion-transmitted B19V infection seems to be a rare or overlooked event, as indicated by data from different European countries. For instance, in the UK, only one case was reported between 1996 and 2022 [25], and in Germany no transfusion-transmitted B19V infection was reported between 1997 and 2017 [26], in the absence of routine testing for this virus in blood donors during this period.

Due to the limited number of transmission cases reported, the exact level of B19V titres that pose a risk of virus transmission through SoHO cannot be adequately assessed.

To reduce the risk of possible B19V transmission by plasma-derived products, the European Pharmacopoeia mandates testing plasma pools for fractionation for B19V using a validated nucleic acid amplification test (NAT). These plasma pools, used in manufacturing, can only contain B19V DNA loads below 10 000 international units (IU) per millilitre. Any final manufacturers' plasma pools exceeding this B19V DNA level must be discarded [27].

Systematic testing of blood donors for B19V infection, in addition to the screening of donations of plasma for fractionation, is not required. However, if a B19V infection is suspected or confirmed for a donor, the B19V-positive blood or blood components should not be transfused to individuals susceptible to severe clinical outcomes of B19V infections i.e. pregnant women, patients with chronic haemolytic diseases or hemoglobinopathies, and immunosuppressed people [28]. Selective screening of donations with NAT to provide safe components for these recipients could be considered [29]. An alternative testing strategy in use in the Netherlands is the selective testing of donors for B19V antibodies to make B19V-tested blood components available for susceptible patients upon request. Donors with two positive B19V (IgG) antibody tests at an interval of at least six months are considered safe for B19V-susceptible recipients [30].

Even though B19V transmission cases through HSC transplantation are seldom reported, regarding the current epidemiological situation, the risk of B19V infections in HSC transplant recipients should be considered.

The new regulation CBTH

Regulation (EU) 2022/2371 on serious cross-border threats to health – **Art. 20**

Where an alert is notified [...] the Commission shall, where necessary for the coordination of the response at Union level [...], make promptly available to the national competent [...] a **risk assessment** of the potential severity of the threat to public health, including possible public health measures. That risk assessment shall be carried out by one or more of the following Union agencies or bodies:

a) the **ECDC** [...] in the case of a serious cross-border threat to health [...], including where it relates to substances of human origin that can potentially be impacted by communicable diseases [...];
b) the European Medicines Agency (**EMA**) [...] where the serious cross-border threat to health is linked to medicinal products and medical devices;
c) the European Food Safety Authority (**EFSA**) [...] in the case of a serious cross-border threat to health [...] falls under the mandate of EFSA;
d) the European Chemicals Agency (**ECHA**) [...] in the case of a serious cross-border threat to health [...] falls under the mandate of the ECHA;
e) the European Environment Agency (**EEA**) [...] in the case of a serious cross-border threat to health [...] falls under the mandate of the EEA;
f) the European Monitoring Centre for Drugs and Drug Addiction (**EMCDDA**), [...] in the case of a serious cross-border threat to health [...] falls under the mandate of the EMCDDA.

The risk assessment shall be carried out [...] in cooperation with the European Union Agency for Law Enforcement Cooperation (**Europol**) where the serious cross-border threat to health emanates from terrorist or criminal activity [...]

What content in RRA for SoHO – organs?

Thank you

Session 10
Topics and ECDC activities identified by the SoHO-Net Organs group
19 June

Session overview

Reflection on topics for the SoHO-Net Organs group and the role of ECDC

1. **Reflection and prioritisation of topics for the SoHO-Net Organs group**

2. **Role of ECDC in ensuring the safety of organs**

3. **Future meetings**

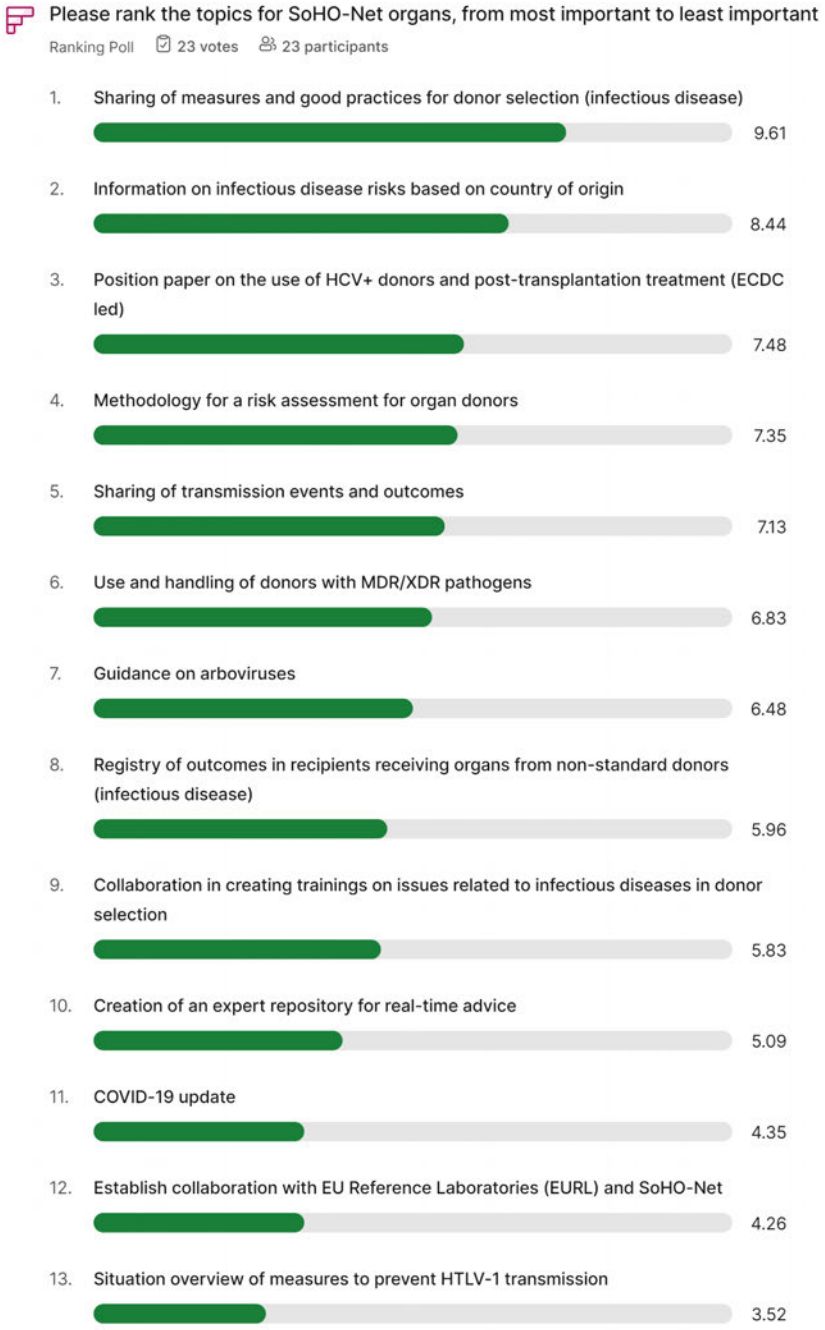
Expectations for SoHO-Net and ECDC in Organs

- Sharing of experience with nonstandard donors in emerging diseases
- Sharing of recommendations and good practices on emerging diseases
- Recommendations on harmonised minimum standards
- Collaboration with other ECDC networks
- Clarify roles of different stakeholders: Notify, VES...
- Leave room for country decisions

Topics for SoHO-Net listed in day 1

- Use and handling of donors with MDR/XDR pathogens
- Guidance on arboviruses
- COVID-19 update
- Position paper on the use of HCV+ donors and post-transplantation treatment (ECDC led)
- Registry of outcomes in recipients receiving organs from non-standard donors (infectious disease)
- Sharing of measures and good practices for donor selection (infectious disease)
- Information on infectious disease risks based on country of origin
- Methodology for a risk assessment for organ donors
- Collaboration in creating trainings on issues related to infectious diseases in donor selection
- Establish collaboration with EU Reference Laboratories (EURL) and SoHO-Net
- Sharing of transmission events and outcomes
- Creation of an expert repository for real-time advice
- Situation overview of measures to prevent HTLV-1 transmission

One final question!



Future network meetings

Meeting	Date
Workshop: Information to be shared in EpiPulse - Virtual	September 2024
EpiPulse hands-on training – Virtual	September 2024
SoHO-Net blood group meeting – Stockholm	4-5 December 2024
SoHO-Net plenary meeting – Virtual	15 April 2025 (not confirmed)
SoHO-Net tissues and cells and MAR groups meeting – Stockholm	30 September – 01 October 2025

Session 11
Closing remarks
19 June

Thank you!

To the NCC, chairs, presenters, and all participants