Tropical and parasitic infections in solid organ transplantation

6th International Congress Infections & Transplantation
Varese Italy 18-20 May 2017.

Wanessa Trindade Clemente
Belo Horizonte, Minas Gerais, Brazil

Nothing to disclosure

Highlights

- The Scenario
- Main Challenges
- Specific Diseases
- Take Home Message

The Scenario

Rare complication even in tropical settings, however they are growing in importance ...

Transplantation	*Geographical exposure*
Increasing numbers of transplants in the tropics Expanded organ acceptance	Travelling to endemic areas Immigration *"Transplant tourism"* Climate changes

- ***"True"* incidence is unknown**
  - Information based on case reports
  - Frequently misdiagnosed
- **Associated with high mortality**

Franco-Paredes et al. Int J Infect Dis 2010
Machado CM & Levi JE. Infect Dis Clin N Am 2012
Lattes R et al. Curr Infect Dis Rep 2012

The Paradigm Shift: Timetable

DDI, reactivation and community acquired

Tropic and parasitic diseases are expected to occur in any period after transplantation

Fishman J AJT, 2017

Which to choose?

- Protozoa
  - Chagas
  - Leishmania
- Virus
  - Dengue fever
  - Yellow fever
  - Zika
  - Chikungunya

Main Questions

- **What are the risks for donors and recipients?**

  Endemic x Non-endemic

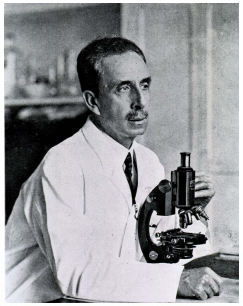
- **How to screen?**

- **Organ acceptance criteria**

- **How do you manage?**

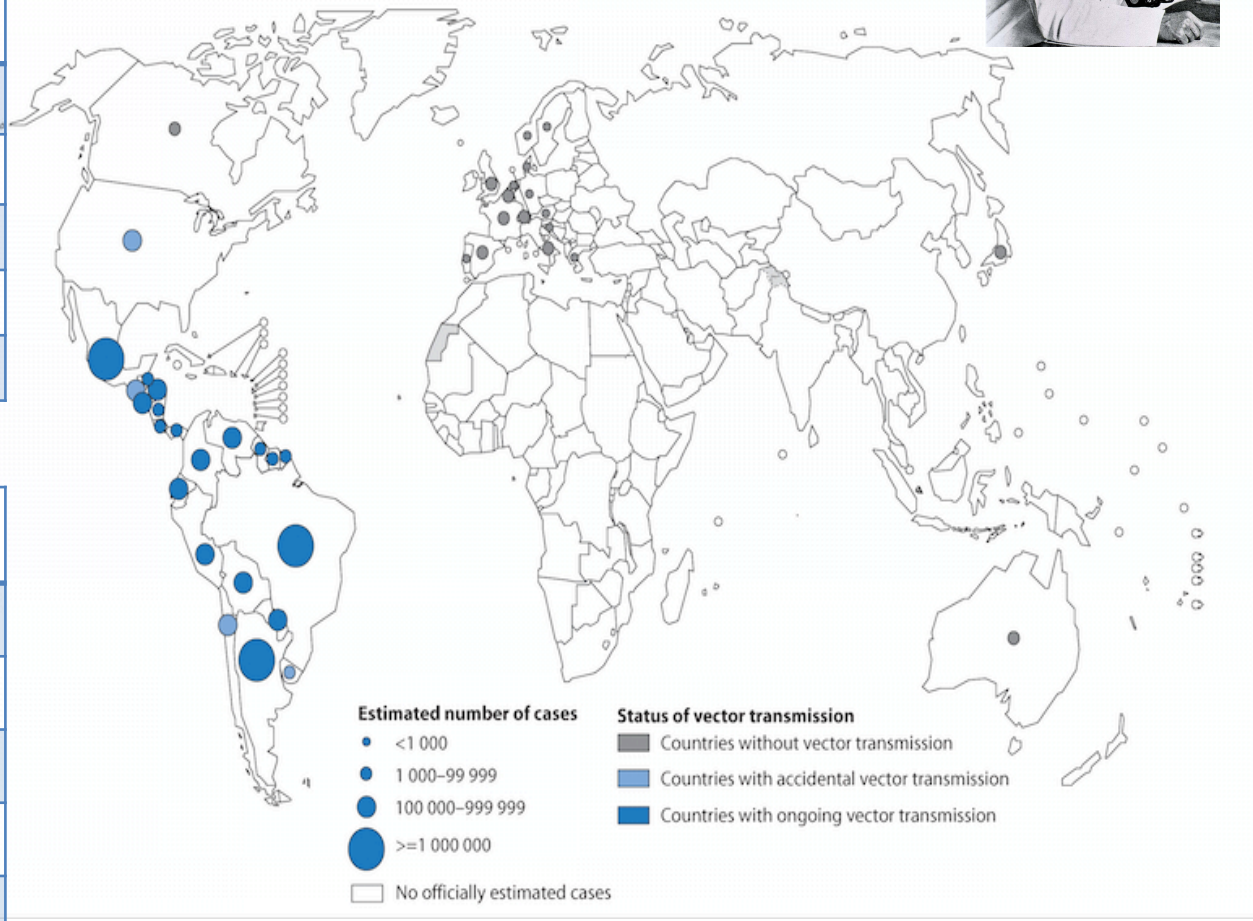
CHAGAS DISEASE

Chagas Disease



Estimated prevalence *T. cruzi*	
Mexico	0.7%
Brazil	1.3%
Colombia	3.9%
Argentina	8.2%
Bolivia	15.4%

Estimated prevalence *T. cruzi-infected* immigrants	
US	2.0%
Europe	2.9%
Canada	3.5%
Australia	3.8%
Spain	5.2%



Protozoan *Trypanosoma cruzi*

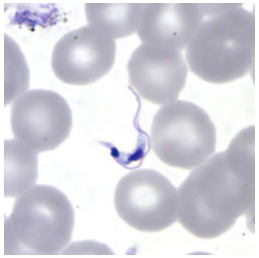
7 - 8 M infected people worldwide, mostly in Latin America countries

WHO-WER 2015. WHO, 2017
Acta Tropica 2010.

Illustrative Case

- 22 yo female admitted 3 mo after KT with **intermittent fever and lack of appetite** during the last 3 days
  - **Pancytopenia** (Hb 5.9 g/dL, WBC 1,600 cels/mm^3 and platelets 90.000)
  - No respiratory symptoms, no visceromegaly, no skin lesions

– **Direct microscopy**: parasites in peripheral blood and bone marrow



Surprise!!
C shape trypomastigote with a proeminent kinetoplast

– **Negative ChD serology**

Courtesy of Dr Ligia Pierrotti
Hospital das Clínicas - USP São Paulo. Renal Transplant Service

The Follow-up

The patient

- BZD 300 mg/day, 60 days (acute ChD) with response (PCR and parasitemia negative).

The donor

- Negative ChD ELISA

Further investigation:

POSITIVE Ch[illegible] here the [illegible]

[illegible]male, died due to hemorrhagic stroke **(Born in endemic area: Pernambuco, Brazil).**

5 mo later and 1 mo after rejection treatment (ATG plus IVIG)

- **Readmitted: fever + cytopeni[illegible] parasitemia = same s[illegible]**
- **ChD relaps[illegible] para[illegible]**

[illegible]th BZD 300 mg/day

Monitoring:

- Negative parasitemia after 2 weeks: PCR and parasitological tests
- Serology (ELISA and TESA-blot): persisted negative **(no seroconversion)**

ChD DDI and reactivation after rejection treatment

What are the risks for recipients?

- **Epidemiological situation:** Endemic x Non-endemic
- **DDI risk:** ~ 10-20% LT and KT.
- **Reactivation:**
  - **Higher for heart > kidney:** HT (27 to 90%) and KT (8 to 22%)
  - Mostly in the 1st y after transplant.
  - **Outcomes are usually similar to those without ChD.**
- **Organ acceptance:**
  - **Yes:** Kidneys and livers chronically infected donors
  - **No: Donors with acute infection + Hearts (DDI>75%) and Intestines.**

Pierrotti et al. Transplantation 2017 in press
Pinazo et al PLoS Negl Trop Dis 2013
Lattes R & Lasala M CMI 2014

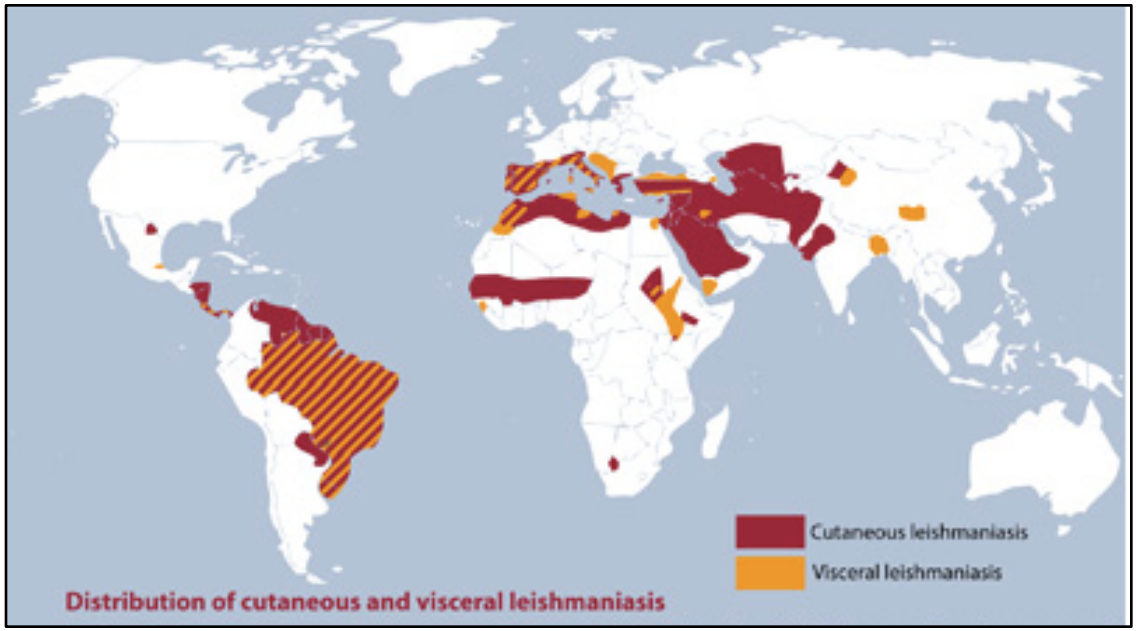
How to screen and manage?

Donor Screening:	For ChD diagnosis:
• Endemic: All donors • Non-endemic: If + epidemiology ➢ TARGET SCREENING At least one single **high-sensitivity and specificity test.**	• At least 2 serological methods (ELISA, IMF and IHA). • **PCR no use as screening test (S: 40 – 95%)** Intermittent parasitemia
Studies on prophylaxis for **D+/R- or R+** are lacking. Consider treatment of the **Living donor**	
Recipients should be monitored for 6 to 24 mo (even if prophylaxis is provided). Routine tests may detect subclinical infection before symptoms. **No study to validate a specific monitoring program.**	
• **Options: Benznidazole* and Nifurtimox.** Cure rate ~ 80%. • If transmission occurs, test weekly until 2 negative results.	

Pierrotti et al. Transplantation 2017 in press
Pinazo et al PLoS Negl Trop Dis 2013
Lattes R & Lasala M CMI 2014

LEISHMANIASIS

Leishmaniasis



Distribution of cutaneous and visceral leishmaniasis

Region	Complex	Species	Clinical Manifestation
Old World	*Leishmania donovani*	*L donovani*	CL, VL, PKLD, ML (rare)
		L infantum	CL, VL (children), PKLD, ML (rare)
		L chagasi	CL, VL (children), PKLD, ML (rare)
	Leishmania tropica	*L tropica*	CL, ML (rare), VL (rare)
		L major	CL, ML (rare)
		L aethiopica	CL, DCL
New World	*Leishmania mexicana*	*L mexicana*	CL, DCL (rare)
		L amazonensis	CL, DCL, ML, VL (rare), PKLD (rare)
		L venezuelensis	CL, DCL (rare)
	Leishmania (Viannia) braziliensis	*L braziliensis*	CL, ML, VL
		L guyanensis	CL, ML
		L panamensis	CL, ML
		L peruviana	CL

WHO, 2010; Kevric, Dermatol Clin 2015 Antinori LID 2008, de Vries Am J Clin Dermatol 2015, Schwartz & Mawhorter AJT 2013, van Griesven CMI 2014; *Aronson,* IDSA CID, 2016

Protozoan disease transmitted through the bite of infected female sandflies.

Broad range of clinical presentation that depends on the species and host.

Mucocutaneous Leishmaniasis

INCIDENCE: 18 cases/100,000 hab

– Few cases in SOT

Visceral Leishmaniasis

INCIDENCE: 2 cases/100,000 hab

Less frequent GP x More prevalent SOT

– *L. infantum chagasi and L. donovani*

– Several cases in SOT

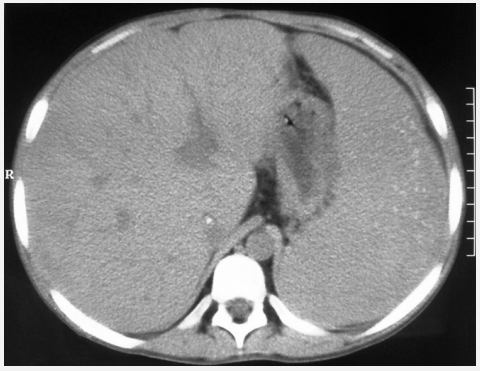
Illustrative Case

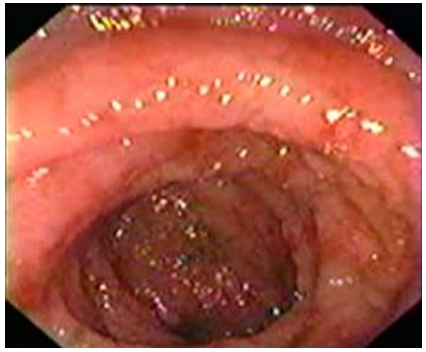
17 yo male, Underwent LT *3 y before.* IS regimen: Steroid + FK.

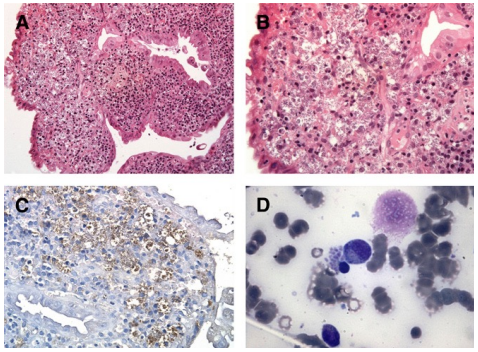
At admission **3 months:** weight loss (3kg) + bloody diarrhea.

Visceromegaly + Pancytopenia, but **no fever**

Negative Anti-*Leishmania* serology *IFAT*







COLONIC LEISHMANIASIS: Atypical presentation

Treatment: LamB 3 mg for 7 days with total resolution of clinical and laboratory findings

Relapse 5 mo after treatment.

Mantained with **secondary prophylaxis:** 3 mg/kg/monthly (18 months)

Araujo et al Am J Trop Med Hyg 2010
Clemente et al Transplantation 2011

The role of asymptomatic carrier in the transmission of *Leishmania*

What is the evidence?

- Up to 70% of blood donors were seropositive for *Leishmania* (serological method and endemic area).
- Few cases of transmission by blood.
- No proved SOT DDI reported

Besides the great number of asymptomatic infections VL remains infrequent

Michel, Acta Tropica 2011
Elmahallawy, TID 2015
Fukutani, BMC Infectious Diseases 2015

LT recipients and donors from an endemic area of VL: mismatch serology/PCR

Laboratory test	LT Recipients (N = 50)	Matched-Liver Donors (N = 17)
Positive IFA (≥ 1:80)	1 (2%)	0
Anti-Leish rK39 rapid test	0	0
Any PCR detection	4 (8%)	4 (23.5%)
Blood	1	4
Liver	3	3
Spleen	NA	1

None of the LT recipients developed VL over 24 mo follow-up. 3 VL cases ~ 830 LT; 2% asymptomatic infection

Clemente et al, AJT 2014

Organs should not be discarded!

How to screen the donors?

Which tests should be performed?	**Donor screening is not recommended!**
Donor acceptance criteria	**Positive serology or previous exposure** • Does not CI donation • Is not recommendation for treatment **Active disease** (Living donor) **should be treated** before donation.
If you accept the organ donor, how to manage?	**Monitor the recipient** • Signs and symptoms • Sequential PCR could be useful

Clemente et al. Transplantation 2017 in press

Visceral Leishmaniasis after SOT

Multicenter survey, 1995 - 2012

Clemente et al 2014 REIPI Network. CMI 2015

36 VL cases (mostly KT: ~ 70%)

Median time post-transplant	11 months (30% < 6mo)

Clinical manifestations

Temperature > 38ºC	86%
Visceromegaly	81%
Cytopenia	47%

Only 1/3 exhibited the triad

Diagnostic methods: Microscopy + Serology

Bone marrow microscopy	81%
PCR	75%
Culture	59%
Serology (IFA + rK39)	76%

Treatment option

Amphotericin B (~ 10 days)	83%
Miltefosine	Treated twice

Relapse after cure	26%
With NO secondary prophylaxis	35%
With secondary prophylaxis	8%

Outcome: Mortality at 30 days 2.8%

Miltefosine

Relapse rate of 20% (6 mo follow-up). Increase dose, duration of treatment and prolonged observation period.

Good option for prophylaxis (?)

Perez-Jacoiste Asín et al TID 2017, Copeland & Aronson Curr Opin Infect Dis 2015
Blum J Travel Med 2014

What is the role PCR?

PCR allow species identification → treatment

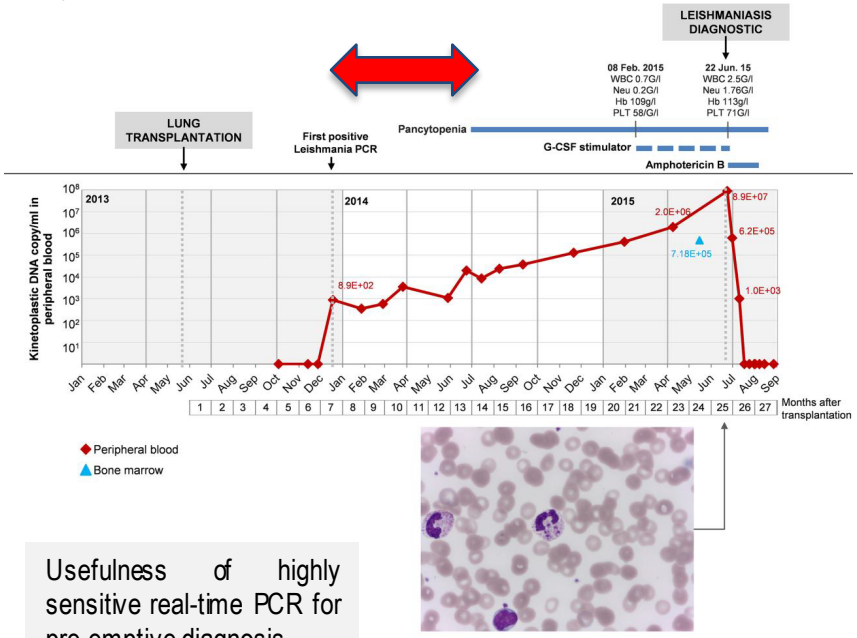
It can be of use

- **pre-emptive approach?**
- **early detection of relapse?**

Persistence of parasite in tissue after treatment does not necessarily represent relapse.

Silva LA et al. Rev Inst Med Trop São Paulo 2013
Moreno EC et al. PloS Negl Trop Dis 2009

Case report: Lung Tx recipient: Positive PCR on PB: months before the development of symptoms



Usefulness of highly sensitive real-time PCR for pre-emptive diagnosis

Opota et al TID, 2016

Leishmaniasis - Recipients

What are the risks?	The higher prevalence of **latent infection in GP** is related to an increased risk **active disease after SOT.**
Which tests should be performed?	The combination of multiple methods is recommended for diagnosis. PCR which may allow species identification and may be positive months before the development of symptoms.
How to manage?	Immunosuppressant dose reduction is recommended **Treatment depends on patient characteristics, Leishmania species, disease extent, drug availability, concomitant infections and previous treatments** Amphotericin B, pentavalent antimoniates, miltefosine, among others.

Clemente et al. Transplantation 2017 in press,
WHO 2010, van Griesven CMI 2014, Paiva-Cavalcanti Cell & Bioscience 2015, Antinori LID 2008, de Vries Am J Clin Dermatol 2015, Schwartz & Mawhorter AJT 2013, van Griesven CMI 2014, *Aronson* IDSA CID 2016.

ARBOVIRUSES

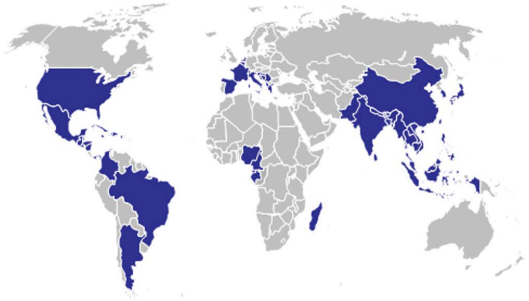
Arboviruses: “arthropod-borne-viruses”

Diseases x Geographical vector distribution

Dengue Chikungunya Zika	*Ae. aegypti* *Ae. albopictus* *Aedes* spp	Mostly urban cycle
Yellow Fever	*Haemagogus* *Sabethes*	Mostly sylvatic cycle
	Aedes spp	Some urban cycle

Ae. aegypti

Ae. albopictus



www.who.int

Urban Arboviruses: Clinical features

Similar early clinical signs and symptoms

	Dengue	Chikungunya	Zika
Incubation period	3 – 15 days (median 6 days)	1 – 12 days (median 5 days)	3 – 12 days
Period of fever	3 – 7 days	7 – 10 days	3 – 7 days
Typical clinical picture	High fever start abruptly, myalgia, headache	Fever and **arthralgia**	Low-grade fever, intense iching, **rash and conjunctivitis**
Rash	30 – 50% cases	50% cases	~100% cases
Leukopenia/ Thrombocytopenia	Yes	Yes	No
Hemorrhage	**Yes**	No	No
Asymptomatic cases	**Up to 75%**	**Up to 25%**	**Up to 80%**

Adapted from Ioos S et al. Medecine et maladies infectieuses, 2014

Urban arboviruses in transplant settings

Seldomly described + similar outcomes + death rates

Dengue

- Several cases among SOT recipients
- Clinical picture and outcome similar to the general population
  - Low risk of DHF due to decreased T-cell responses?

Azevedo LS et al. TID 2011. Fernandes PF et al. Poster ABTO 2013 Congress. RJ - Brazil. De Souza GR et al. Oral presentation ABTO 2013 Congress. RJ - Brazil. Pierrotti LC et al. Oral presentation ICAAC 2015, San Diego, US. Costa SD et al, Am J Trop Med Hyg 2015.

Chikungunya

- Few cases among SOT recipients
- Apparently with less complications and chronic arthralgia

Dalla-Gasperina D et al, TID 2015. Pierrotti et al, TTS 2016 Congress - HK Poster ID #2691. Pierrotti et al, XV Congresso Luso Brasileiro de Transplantação 2016

Zika

- Very few cases
- Clinical picture and outcome apparently similar to the general population

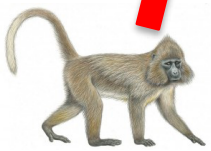
Nogueira ML et al, AJT 2016. Barjas-Castro et al, Transfusion 2016

What we still don't know: The impact of immunosuppression and the need of adjustments? The influence of overlapping diseases? Viruses shedding pattern?

Vectorial and Non-vectorial Transmission

Vector

Besides vector transmission, other routes...

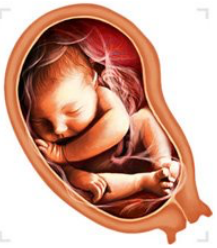


Animal bites

Sexual (ZIKV)

Blood + Organ

Accidental Laboratory Exposure



Vertical

With and without related birth defects.

Maroun-Ortiz Ginecol Obstet Mex 2014
Dotters-Katz SK et al Obstet Gynecol Surv, 2015. Mlakar et al NEJM 2016

Thus the presence of virus RNA mean transmission?

Risk assessment

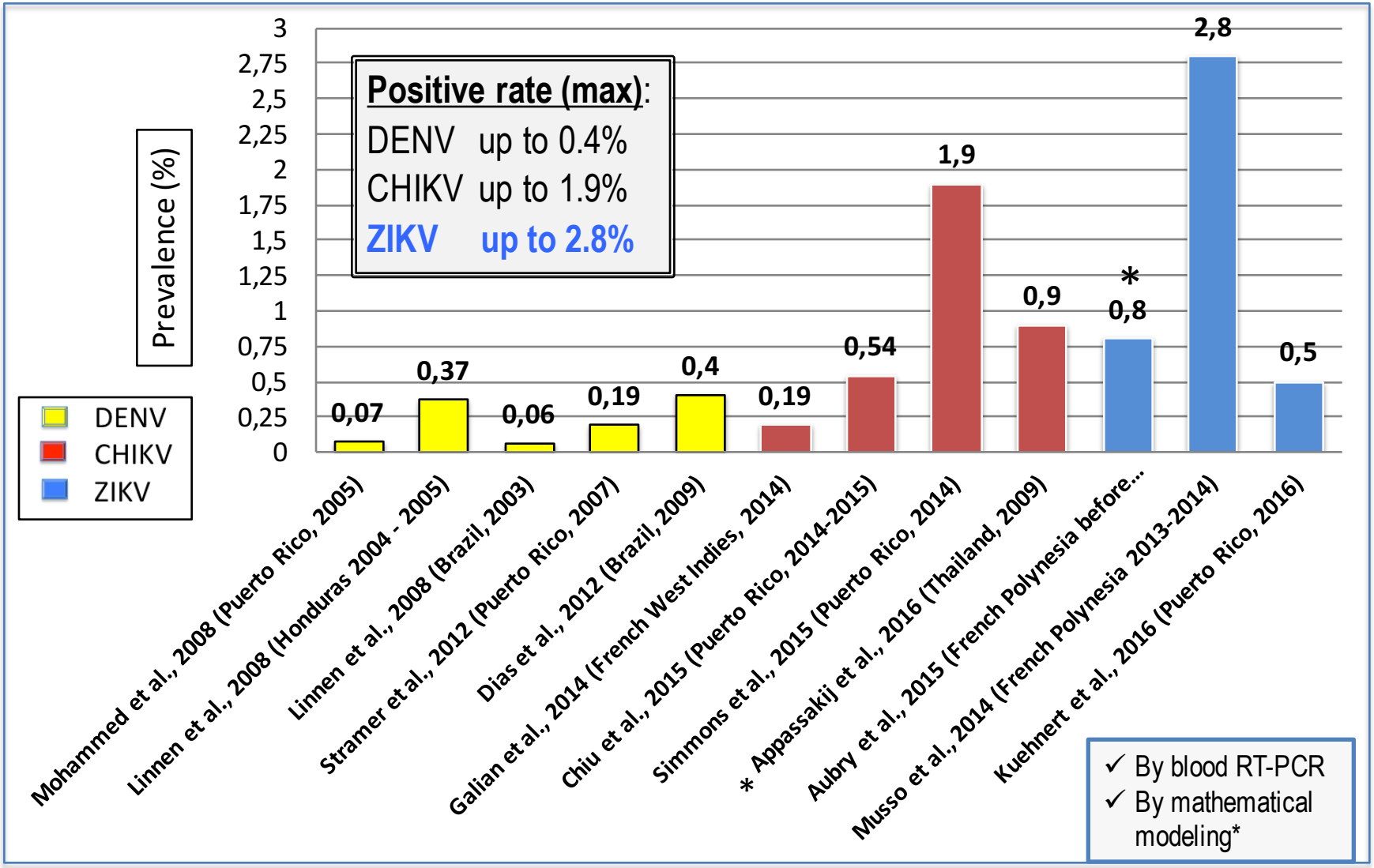
There is not enough knowledge to forcast…

- The **viruses are present in blood up to 2-3 weeks** after a infected-mosquito bite
- The viruses **persist in tissue** after clearance from the blood
- **Asymptomatic infection** allows the donor to pass through the filter of clinical selection
- **High viremic titers** are seen in asymptomatic patients
- Some samples containing virus **RNA can be cultured**

Nogueira RM et al Emerg Infect Dis 2005. Limonta D et al, J Clin Virol 2007. Duffy MW et al, NEJM 2009. Chuang et al, Hong Kong Med J 2008. Stramer SL et al, Transfusion 2012. Musso D et al, Euro Surveill 2014. Póvoa TF et al, PLoS One 2014. PAHO. 1 December 2015 – Epidemiological Alert.

The persistence of ZKV in body fluids have been reported to last longer in urine and semen (Kidney transplantation ?) Paz-Bailey et al NEJM, 2017.

Estimated Prevalence of Asymptomatic Viremia in Blood Donors for DENV/ CHIKV/ ZIKV



Illustrative Case
Blood DDI Transmission (ZIKV)

The Recipient:

- **55-yo male**
- Hepatocellular carcinoma
- **Underwent to LT** from a DD
- **Received pool platelet concentrate one day after LT**

The Blood Donor:

- 54-yo male who was a **repeat** blood donor
- **3 days after donation**: contacted the center reporting **fever, malaise and headache** since 2 days after donation
- On physical exam: **no rash and no conjunctivitis**

ZIKV RT-PCR detected in blood: donor and LT recipient

LT recipient: develop no symptoms related to ZIKV infection

Cunha MS et al., Genome Announc 2016
Barjas-Castro ML et al. Transfusion 2016

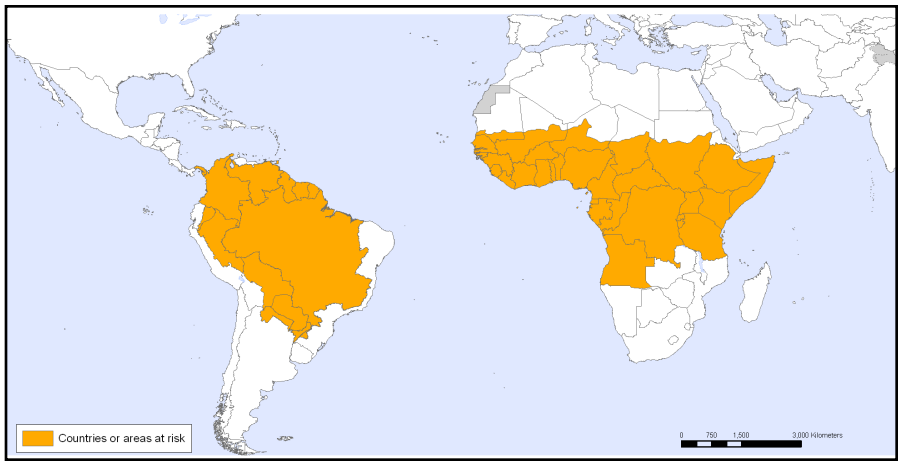
Organ DDI Transmission

What do we really have?

Virus	Source of Transmission	Outcome	Reference
Dengue	Blood transfusion HSCT Organ (Liver)	N:6 Favorable in most cases. **Death reported in HSCT**	Tambyah, NEJM, 2008. Chuang , Hong Kong Med J 2008. Stramer, Transfusion 2012. Rigau-Peres Am J Trop Med Hyg 2001. Punzel Emerg Infect Dis 2014. Gupta J Clin Exp Hepatol 2016
ZKV	Blood products	N: 3 Good outcome	Brazilian Health Regulatory Agency - ANVISA
CHKV	Positive CHIKV RNA in corneoscleral rims	N: 4/12 **Potential risk**	Couderc T JID 2012. **SP donors with + IgG apparently do not transmit CHKV.**

There are only a few cases of proven DDI transmission, usually with favorable outcome.

Yellow Fever



Flavivirus (like Zika, Dengue, and WN)

500 M people at risk in Africa and ~ 400 M in LA

High case-fatality rate

WHO, 2017. JAMA Lucey, 2016.

Recent and ongoing outbreak in numbers...

Brazilian Outbreak Dec 2016 to Apr 2017	
Suspected cases	2900
Confirmed cases	681
Discarded	1451
Under investigation	768
Case fatality rate	34%

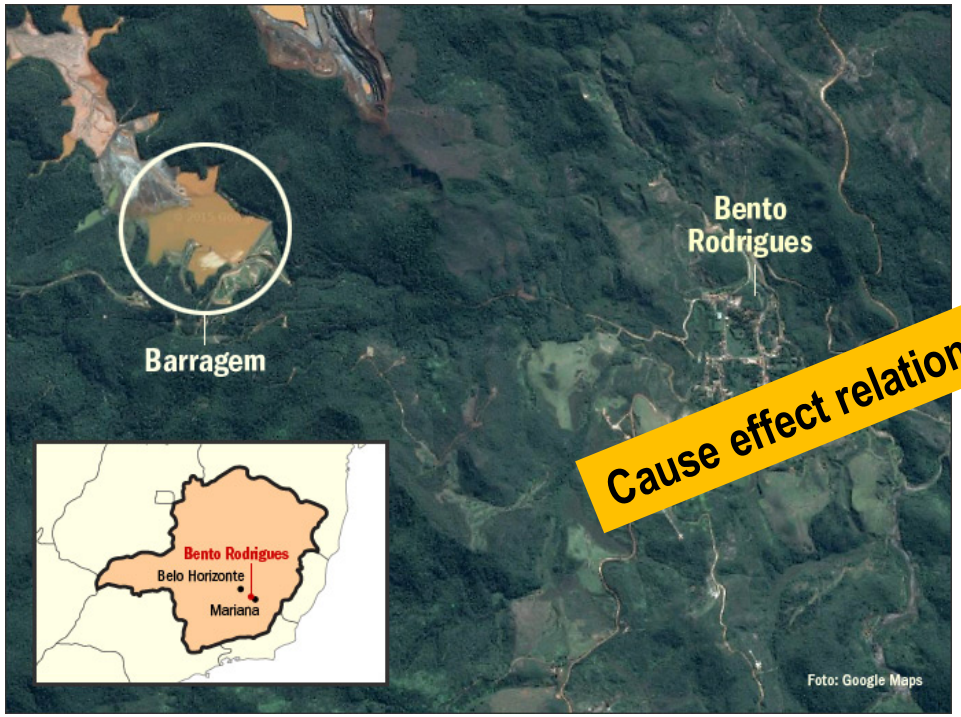
Brazil: Sylvester transmission (no urban described cases since 1942).

PAHO/WHO Epidemiological update April, 2017. Erika Valeska Rosetto. Rev Inst Med Trop São Paulo, 2017

Mining Disaster (Samarco company)
November 2015

Concidently nearly one year ago the rupture of a dam caused the contamination of a major river (Rio Doce river) in MG, in the same area that the outbreak started.

Ecosystem Imbalance: Rio Doce basin



Cause effect relationship is under investigation!

YF in Transplant Setting

- **No reported cases in transplant recipients**
- YF vaccine: live attenuate strain
  - **Not recommended to immunocompromised**
  - Recommended before transplantation

Kotton C. Curr Opin Organ Transplant 2012
Danziger-Isakov et al AJT 2013
Kotton et al AJT 2013

- **Transmission related to transfusion after YFV (CDC MMWR, 2010)** → Temporary defer donation after live virus vaccine (at least 2 weeks)

Brazilian recommendations (ANVISA/MS no.001/2017): 4 weeks after vaccination for blood and organ donation; 6 months for cells and tissues.

Illustrative Case

YF patient as a potential candidate for LT?

41 yo woman from a rural area of Caratinga-MG, admitted to emergency room presenting **gastrointestinal bleeding after one week of febrile ilness**.

History of **abuse of alcohol** in the past.

YF Vaccination status: unknown

At 3rd day of febrile illness: YF IgM serology: negative.

In the hospital:

24h after admission: YF IgM serology: positive/ YF PCR in house: positive

Severe hepatitis: liver enzymes 2,665/14,533 (ALT/AST) with acute liver failure: MELD > 30. Encefalophathy grade 3.

Should LT be indicated in fulminant hepatitis secondary to YF?

Phase 1: Viremic

Remission

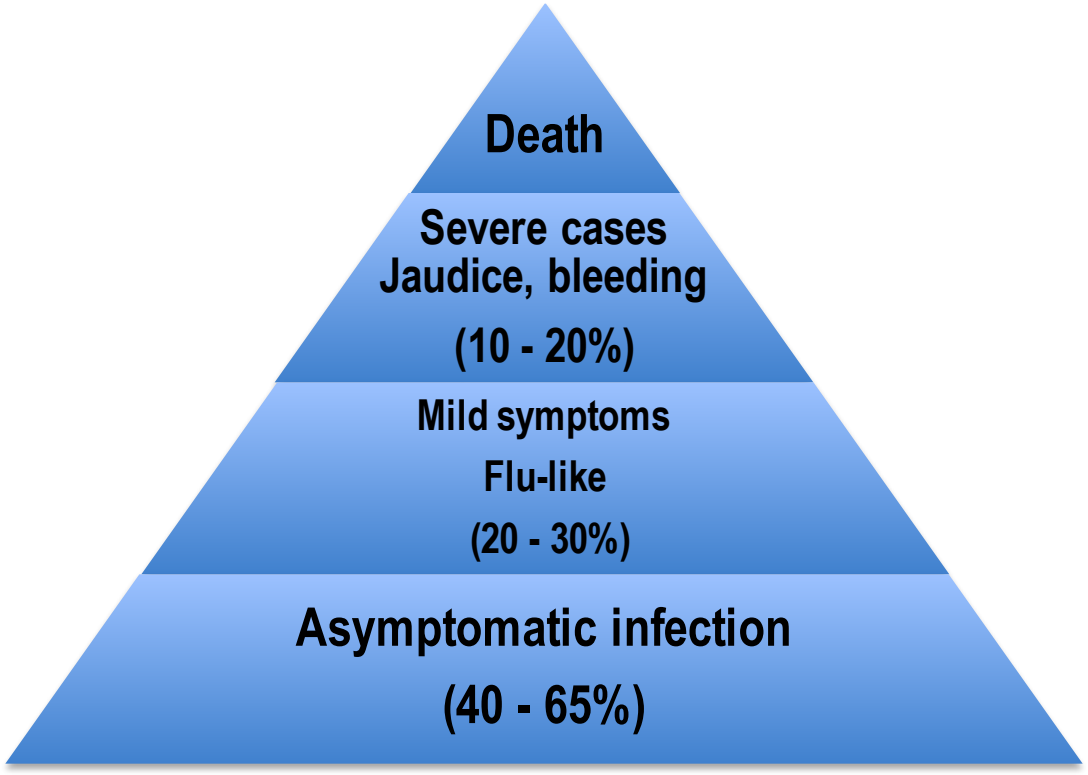
Phase 2: Toxic

Recovery or Death

Fulminant hepatitis: occur during the toxic phase

Is there a risk of persistent viremia after transplantation?

Not known!!



Monath T LID, 2001

Safety donation strategies and management are defined by epidemiological situation and need continuous adaptation

Strategies	Endemic	Non-endemic
What are the risks?	Need to be alert to any symptoms pre and after donation (for living donors).	Travellers returning from endemic regions.
Which tests should be performed?	**Clinical screening** **Viremia screening using NAT** • does not replace clinical screening for recent infection: arbovirus can persist in tissue after clearance from blood!	**Epidemiological screening** • exclude if recent travel Living donors should be educated to avoid infection prior to donation
Donor acceptance criteria	**Discard donors with suggestive of recent arbovirus infection.**	
Temporary defer (living donors)	Usually shorter period **Ex: 30 d if medical diagnosis of ZIKV**	Usually longer period **Ex: 6 mo if medical diagnosis of ZIKV**
How do you manage?	Serology and/or molecular testing. **RT-PCR is considered the gold standard** (due to serological cross-reactions between the same family) **Vaccine: DENV and YV vaccines uses live attenuated strains and are CI for SOT recipients**	

Morris M et al. Transplantation, 2017 in press

Take Home Message

- Tropical diseases in SOT are still a big challenge!
- There are gaps of knowledge in infectivity and disease development
- Vector-borne diseases depends on very complex eco-social conditions for emergence and spread.
- Endemic and non-endemic areas should be assessed in different ways, but only with mutual cooperation of experience and tools, we will be prepared to recognize and manage these diseases.

We are living in a globalized world: people and diseases have no boundaries.

Thank you for your attention

Spero che oggi non sia un addio ma un arrivederci!

Hospital das Clínicas, Faculty of Medicine

Federal University of Minas Gerais (UFMG)

Transplant Infection Commission of the Brazilian Organ Transplant Association (ABTO)

Transplant Infection Commission of the Transplant National System

ESGCIH ESCMID Study group

Acknowledgments: > 50 authors

1. Arboviruses
Michele I. Morris, USA.
Paolo Grossi, Italy.
Mauricio L. Nogueira, Brazil.
Luiz S. Azevedo, Brazil.

2. Chagas Disease
Lígia Pierrotti, Brazil.
Camille Kotton, USA .
Noemia Carvalho, Brazil.
Jimena Amorin, Uruguay.
Julio Pascual, Spain.
Rogelio López-Vélez, Spain.

3. Endemic Fungal infections
Edson Abdala, Brazil.
Rachel Miller, USA.
Alessandro Pasqualotto, Brazil.
Patricia Muñoz, Spain.
Arnaldo Colombo, Brazil.
Manuel Cuenca-Estrella, Spain.

4. Visceral and Cutaneous Leishmaniasis
Wanessa Clemente, Brazil.
Paulo Henrique Orlandi Mourão, Brazil.
Francisco Lopez-Medrano, Spain.
Brian Schwartz, USA.
Carmen García-Donoso, Spain
Julian Torre-Cisneros, Spain.

5. Malaria
Ligia Pierrotti, Brazil.
Marilyn Eckstein Levi, USA.
Silvia Maria di Santi, Brazil.
Aluísio Segurado, Brazil.
Eskild Petersen, Denmark.

6. Schistosomiasis and Strongyloidiasis
Luis F. Camargo, Brazil.
Nassim Kamar, France.
Eduardo Gotuzzo, Peru.
Alissa Wright, USA.

7. Traveler's diarrhea
Nicholas J. Beeching, UK
Jordi Carratalà, Spain
Raymund Razonable, USA
Isabel Oriol, Spain
Eduardo Vilela, Brazil

8. Tuberculosis
Guilherme Santoro-Lopes, Brazil.
Aruna Subramanian, USA.
Israel Molina, Spain.
José María Aguado, Spain.
Ricardo Rabagliatti, Chile.
Oscar Len, Spain.

9. Vaccines
Raquel Stucchi, Brazil.
Marta Heloisa Lopes, Brazil.
Deepali Kumar, Canada.
Oriol Manuel, Switzerland.

10. Viral Hepatitis
Luciana Costa Faria, Brazil.
Débora Terrabuio, Brazil.
Hakan Leblebicioglu, Turkey.
Shirish Huprikar, USA.

11. MAPS
Paulo Henrique Mourão, Brazil
Joan Gavalda, Spain
Fernando Salvador, Spain
Israel Molina, Spain

Recommendation for suplementary reading!

C'mon guys, we'll find someone with the answers.
Just keep looking.