



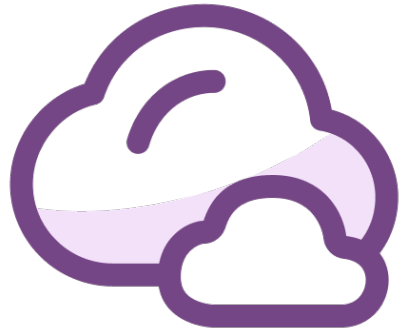
GenEpi-BioTrain - Virtual training 8 - Waterborne disease and Water Surveillance

# Leptospirosis

Mathieu Picardeau, Institut Pasteur  
July 23th, 2024

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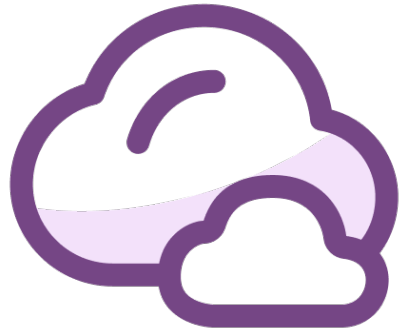


**In which field do you work?  
medical, public health,  
veterinary, research, education,  
industry, etc**

① Start presenting to display the poll results on this slide.

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**What country are you from ?**

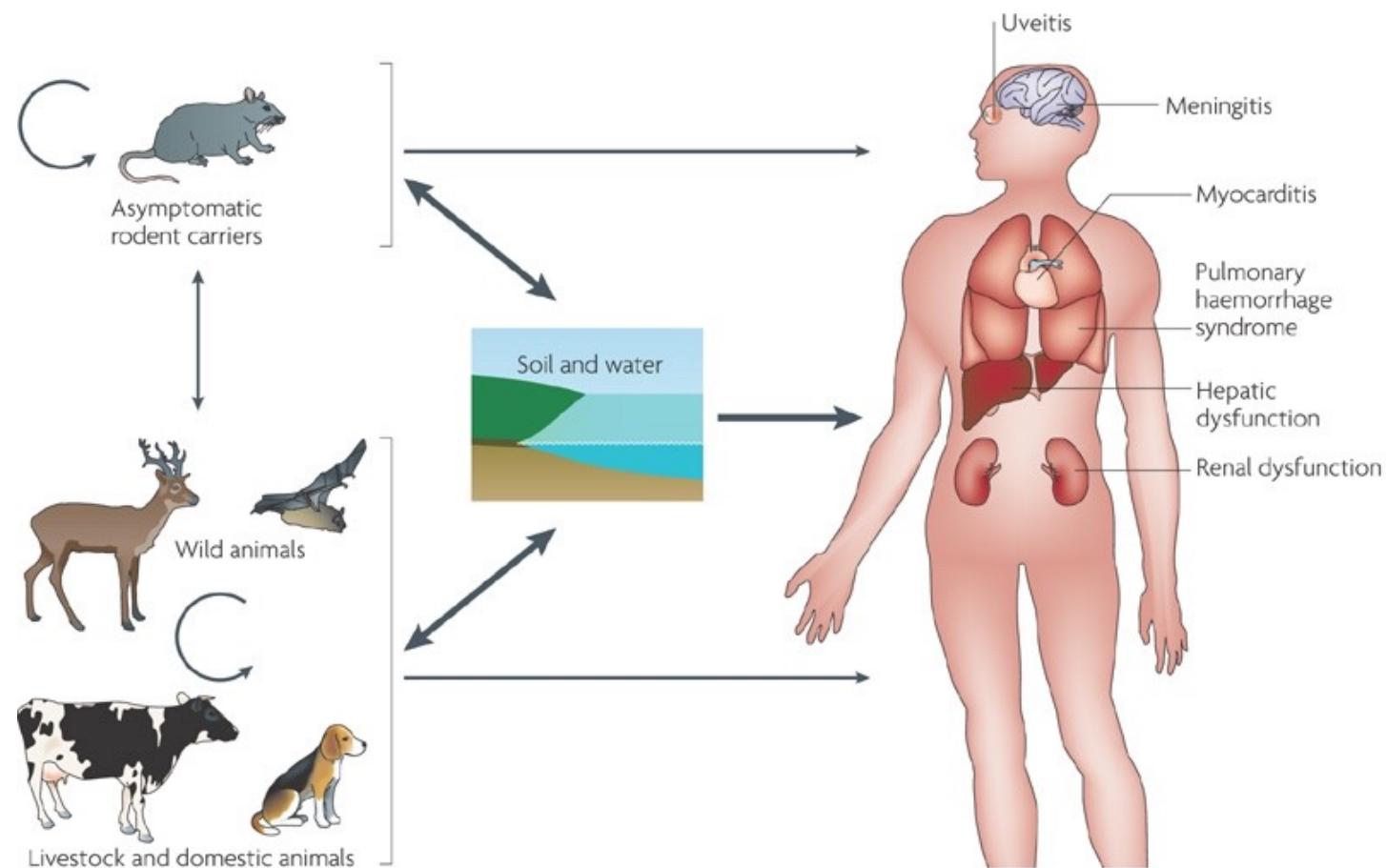
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# Outline

This session consists of the following elements

1. Epidemiology of leptospirosis
2. Diagnosis of leptospirosis
3. Preventive measures
4. *Leptospira* : taxonomy and typing tools
5. Conclusions
6. Group exercise (Jean-François Mariet)

# The cycle of leptospirosis



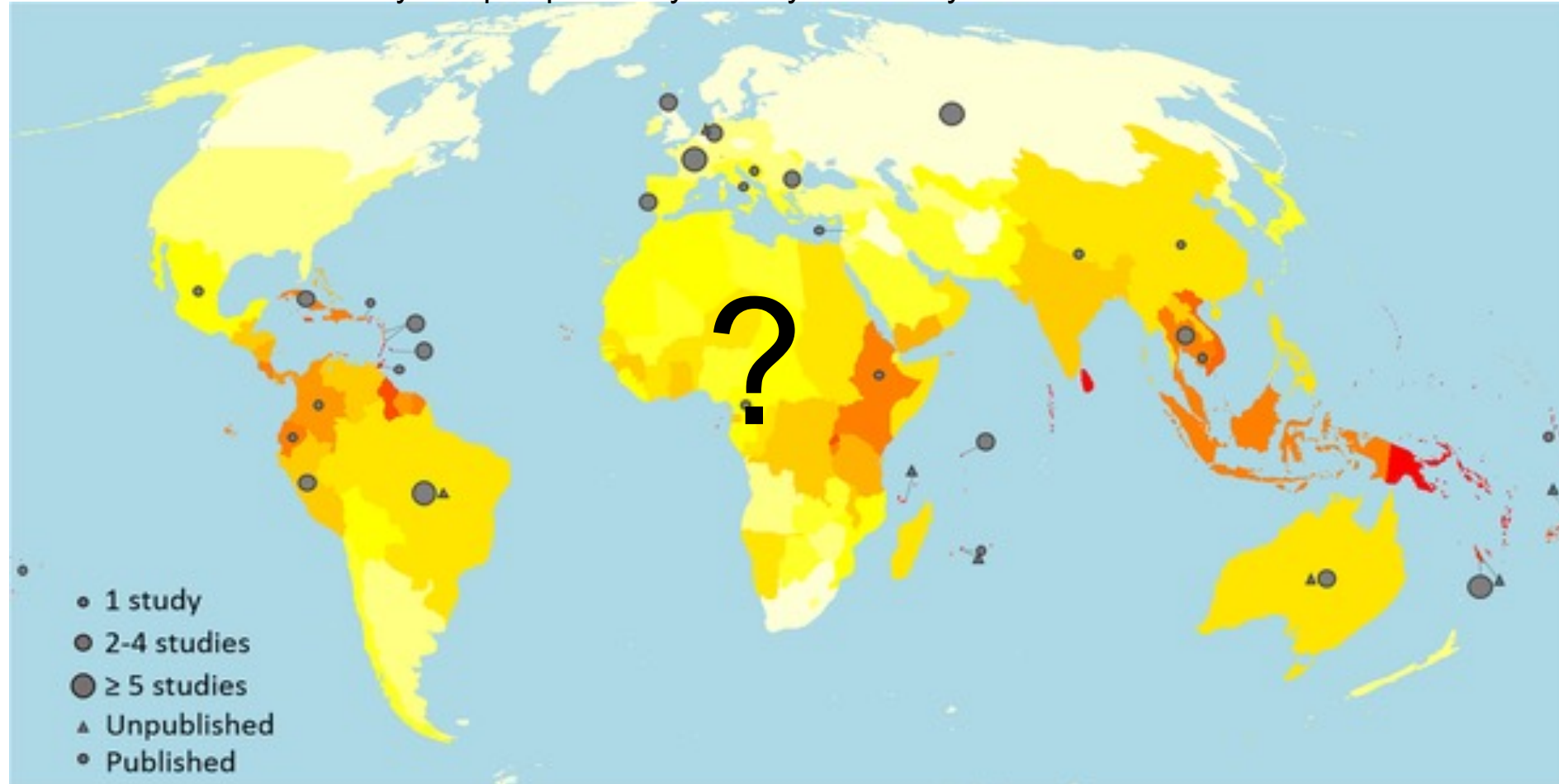
## Differential diagnosis

- Influenza
- Hepatitis
- Meningitis
- Yellow fever
- Viral haemorrhagic fever
- Dengue fever
- Malaria
- Hanta virus
- Lyme disease
- Rift valley fever
- Legionellosis
- Nipah and Hendra virus
- Plague
- Typhoid fever
- Brucellosis
- Q fever
- Toxic shock syndrome
- COVID 19

# Global burden of leptospirosis

> **1 million severe cases and 60,000 deaths due to leptospirosis / year**

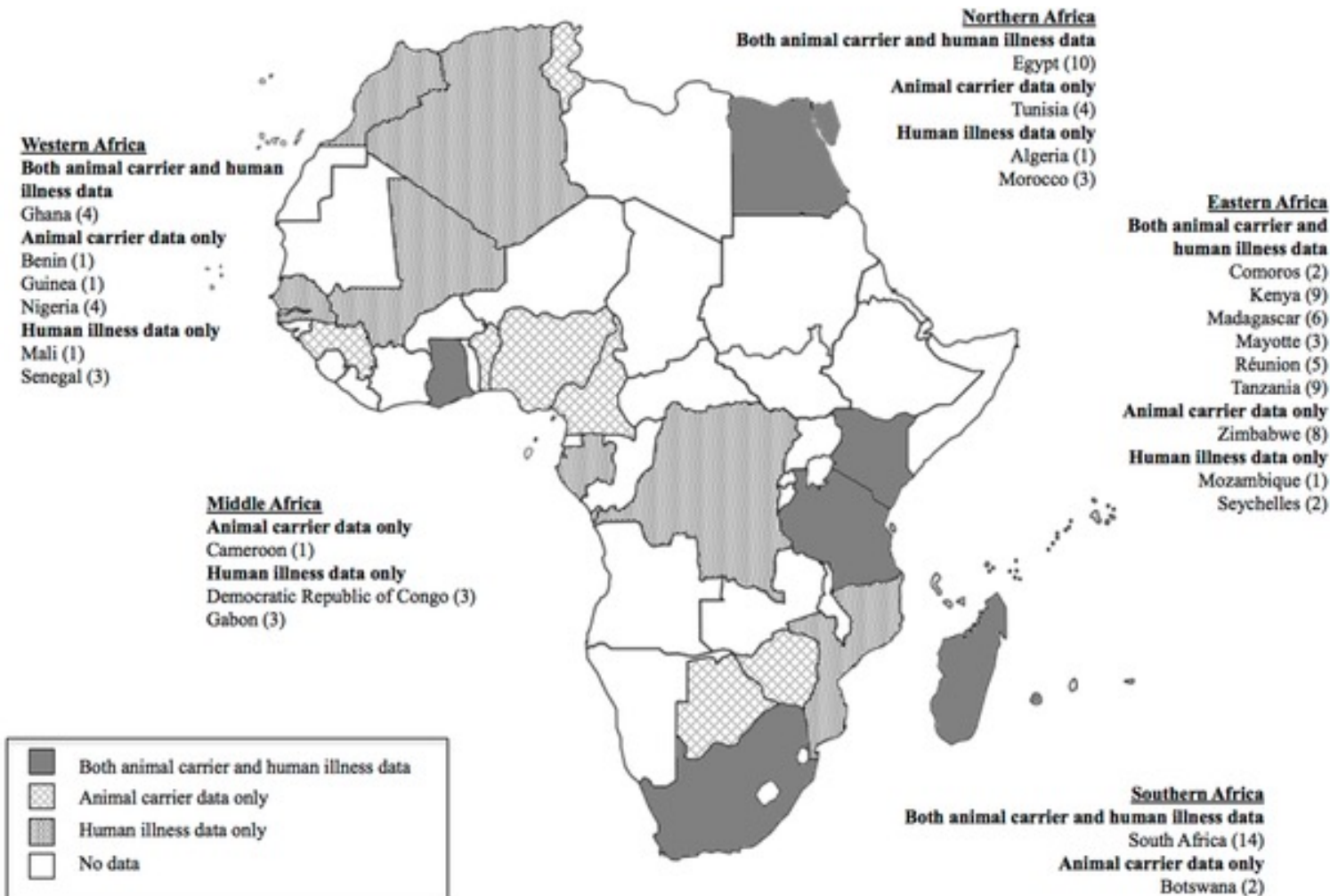
Estimated annual morbidity of leptospirosis by country or territory



Annual disease incidence is represented as an exponential colour gradient from white (0–3), yellow (7–10), orange (20–25) to red (over 100), in cases per 100,000 population.

# An under-recognized cause of acute fever

- Increasing evidence that leptospirosis accounts for a significant proportion of nonmalarial fever cases



Allan *et al.* 2015

# Leptospirosis, a neglected and emerging disease

## Neglected disease

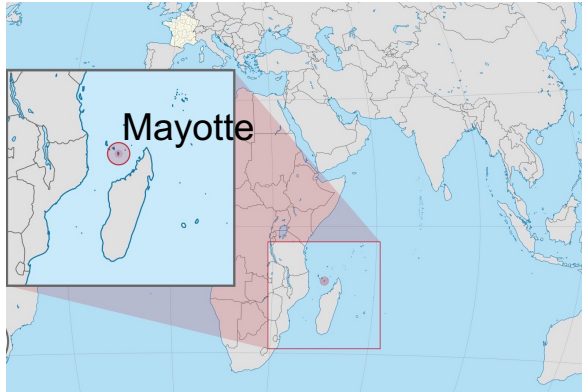
- Limited information on disease burden
- Affects the most neglected and marginalized populations
- Lack of adequate diagnostics
- No effective control measures
- Universal vaccines are not available
- Limited understanding of the epidemiology and pathogenesis

## Emerging disease

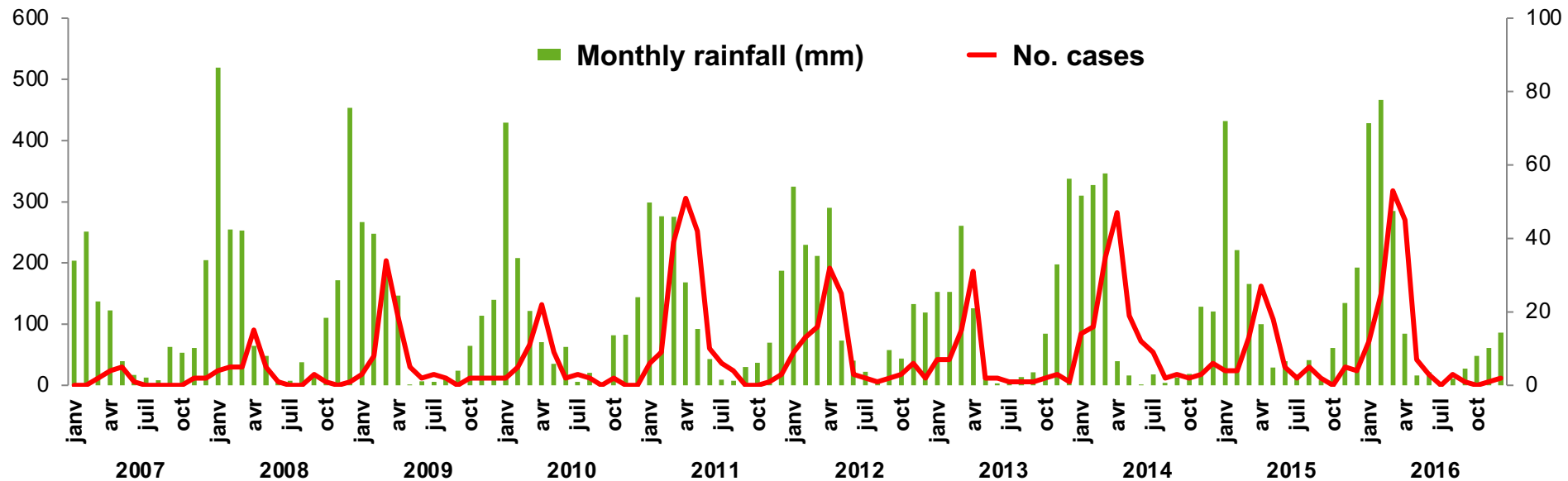
- **Demographic / ecologic changes**
  - One billion individuals live in slums (rat-borne transmission)
  - The urban slum population will double in the next 25 years
- **Climatic changes**
  - Global warming
  - Extreme climatic events (heavy rainfalls, etc)



# Annual Rainfall-Associated Epidemics of Leptospirosis

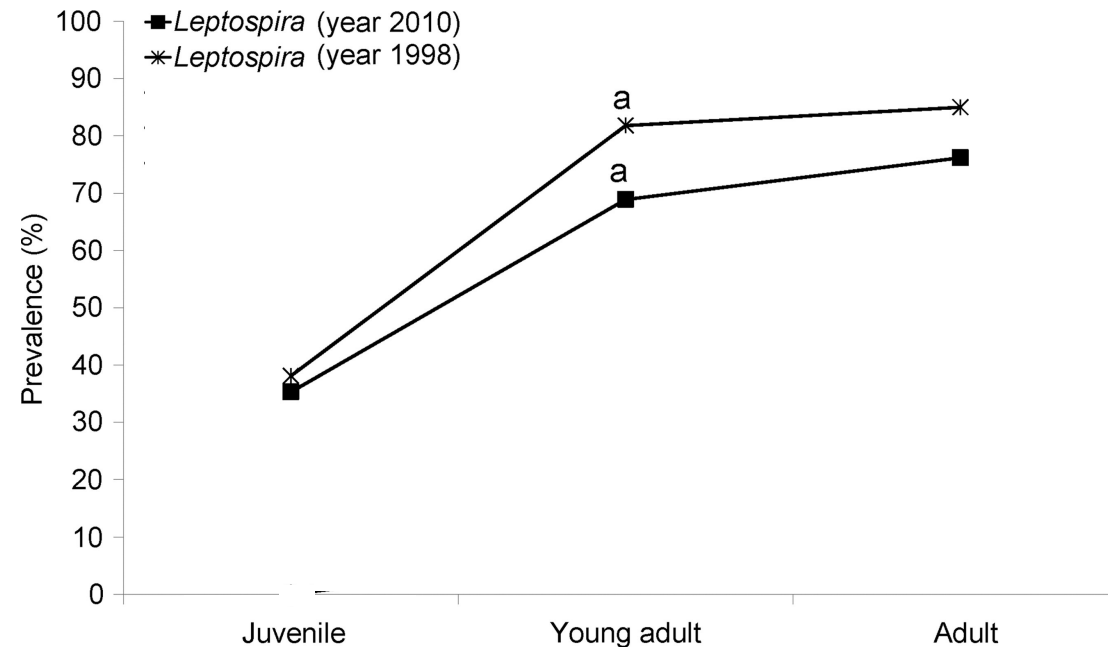


- Mayotte
- 101st French Department
- Indian Ocean
- ~200,000 inhabitants



# Leptospirosis in favelas

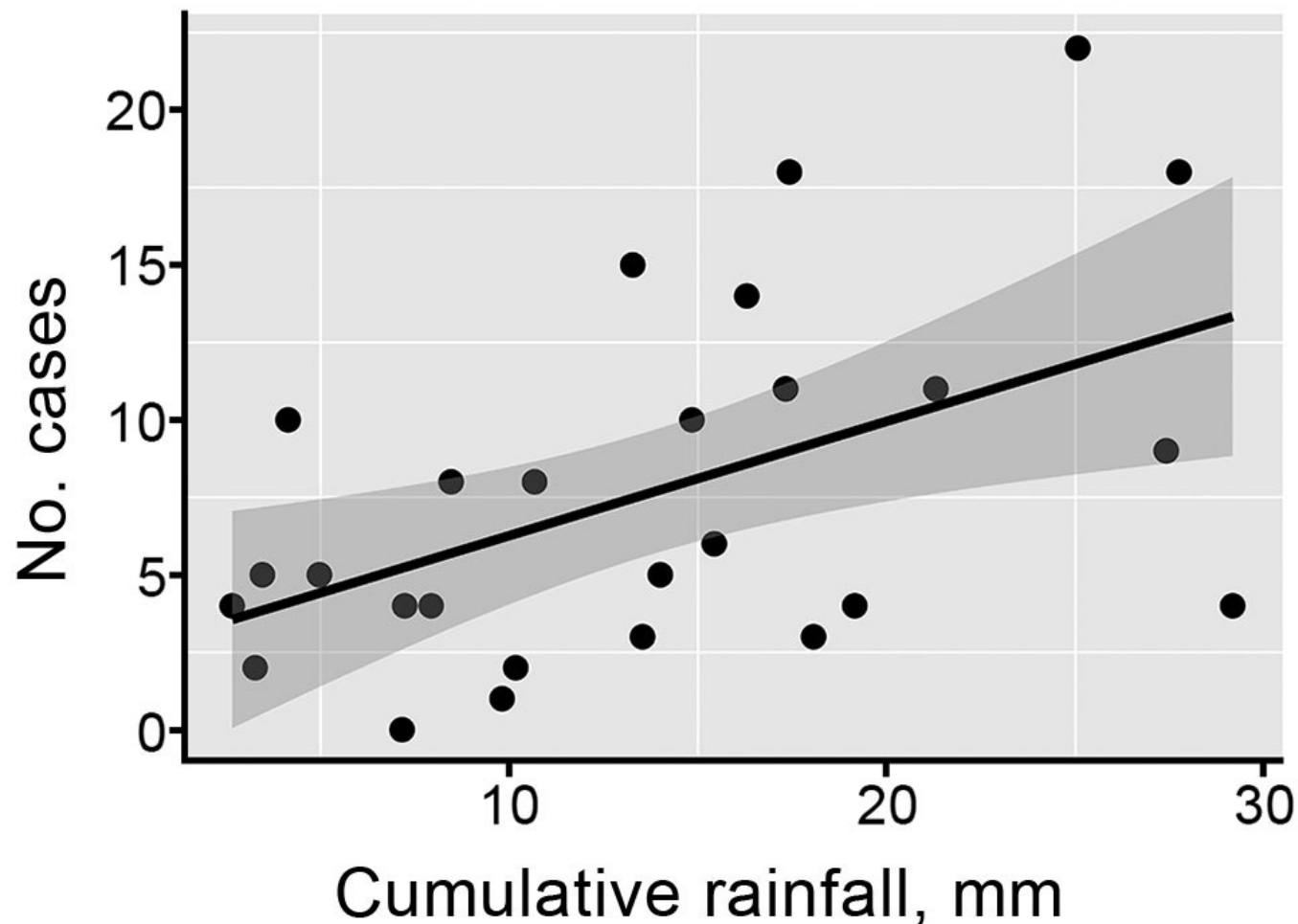
## Prevalence for three age groups of rats



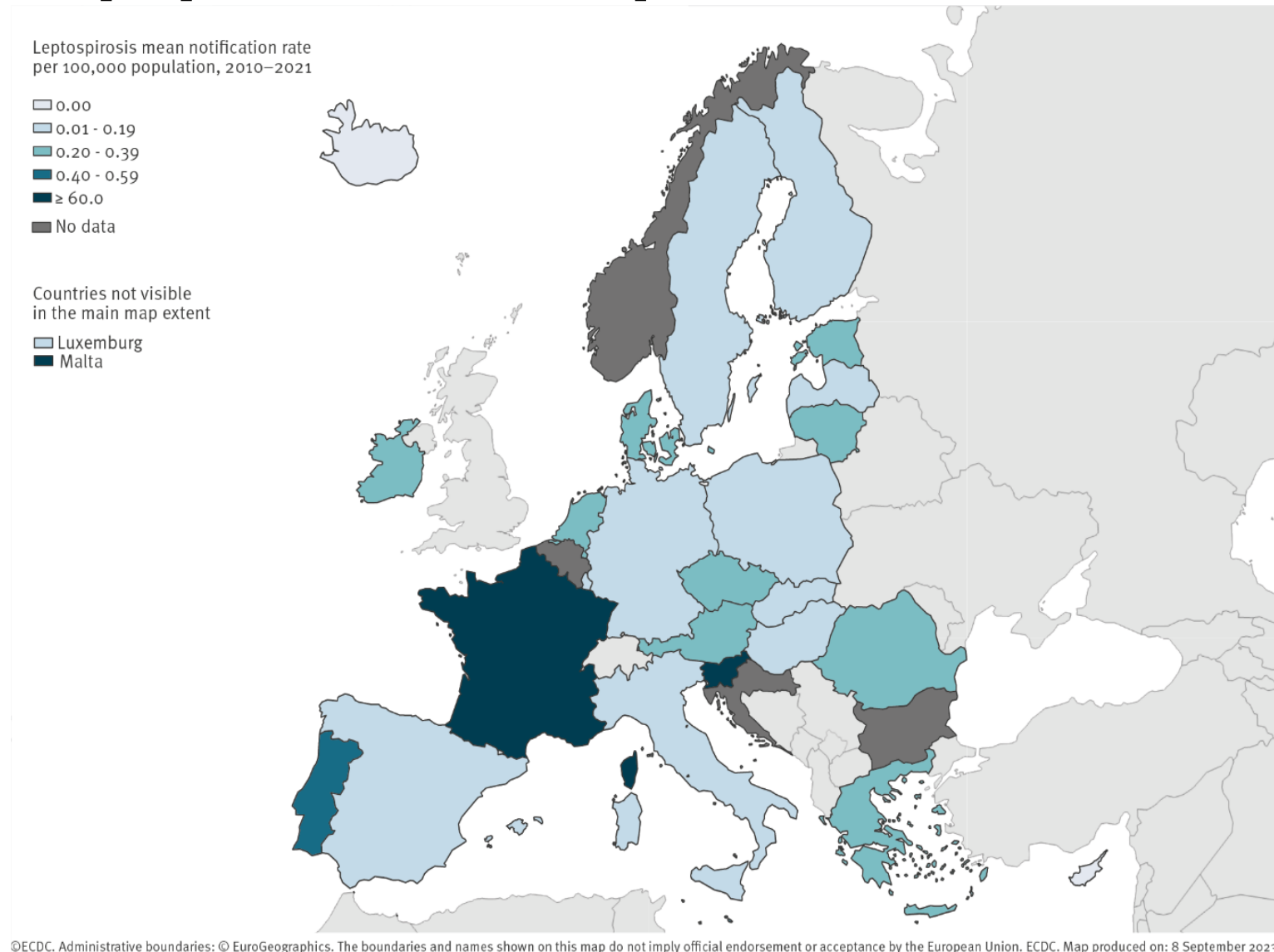
Costa *et al.* 2014



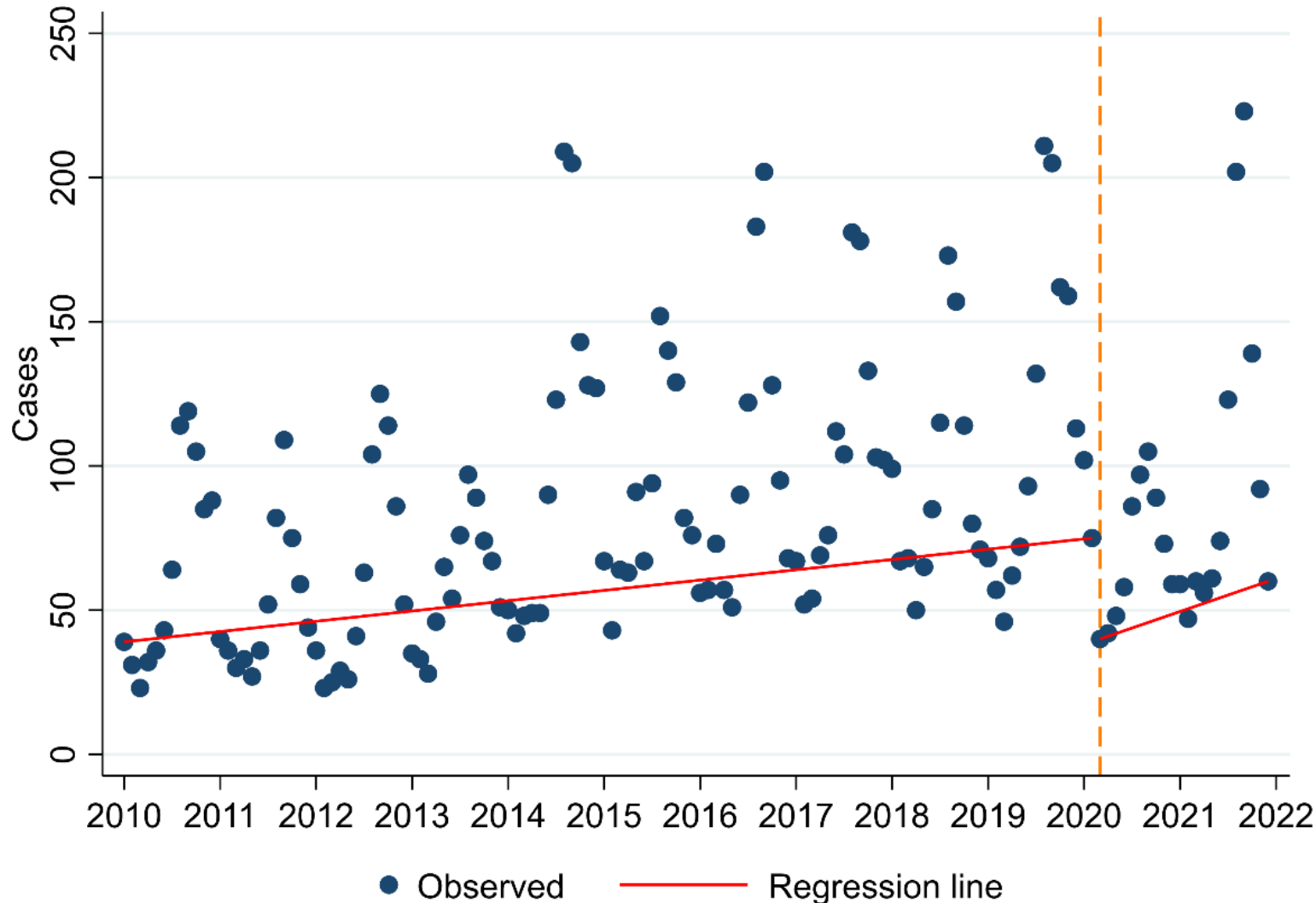
# Correlation between cumulative monthly rainfall and monthly citywide cases of leptospirosis requiring hospitalization, Salvador de Bahia, Brazil



# Average annual rate of confirmed leptospirosis cases per 100,000 population, Europe, 2010–2021



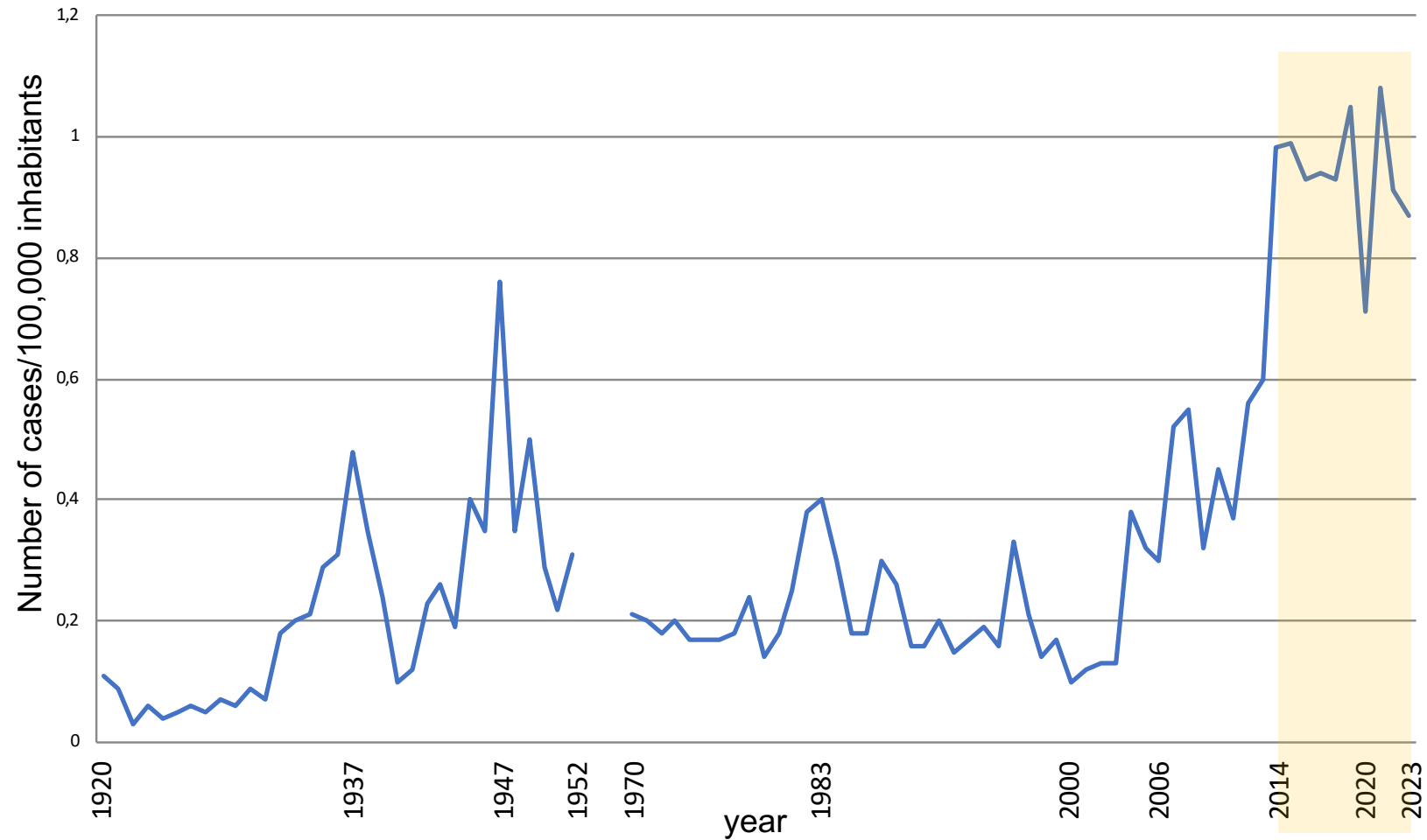
# Monthly number of confirmed leptospirosis cases by month, Europe, 2010–2021 (12 180). 23 countries



Beaute *et al.* 2024

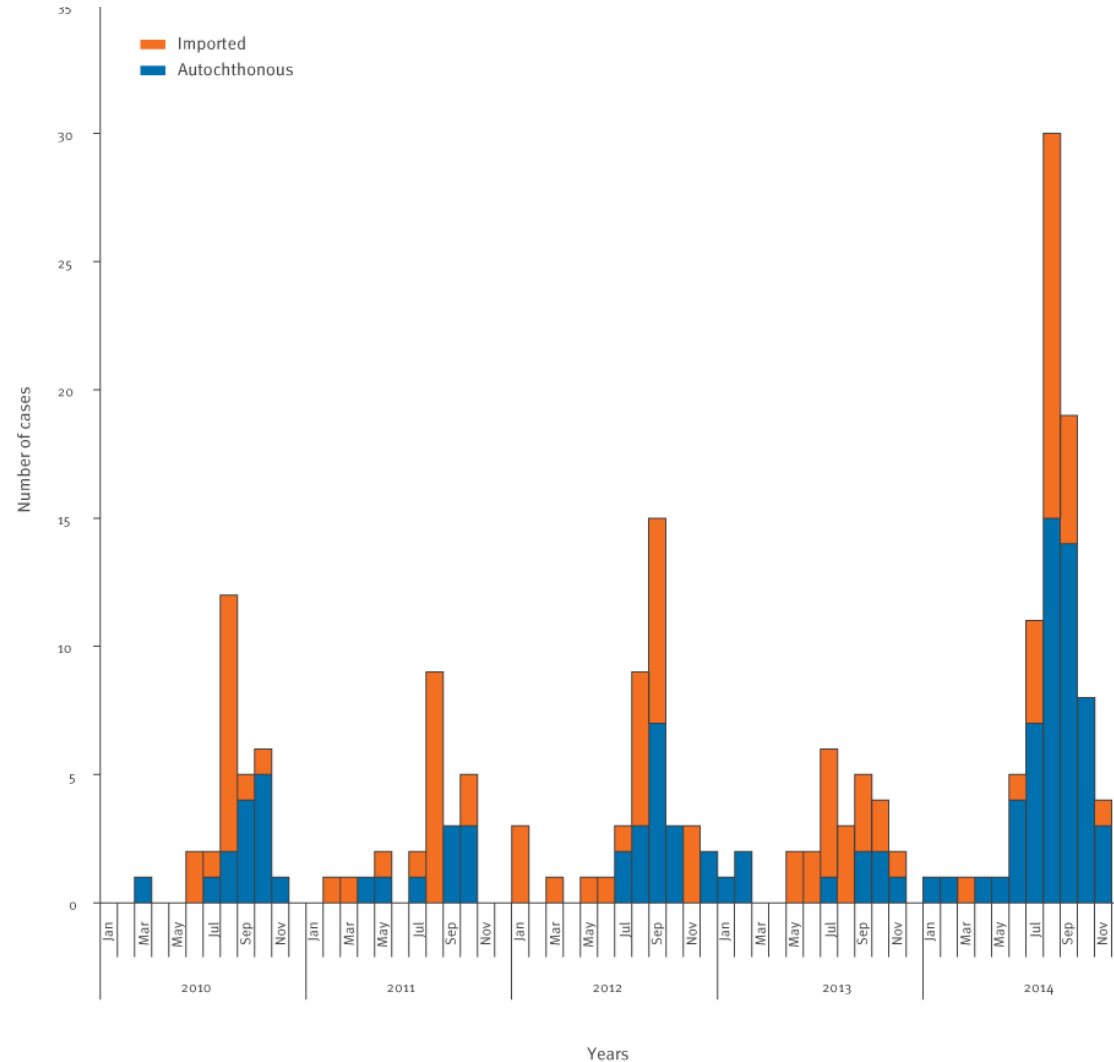
# Leptospirosis in Mainland France, 1920-2023

(data from the NRC for Leptospirosis, Institut Pasteur)



# Marked increase in leptospirosis infections in humans and dogs in the Netherlands, 2014

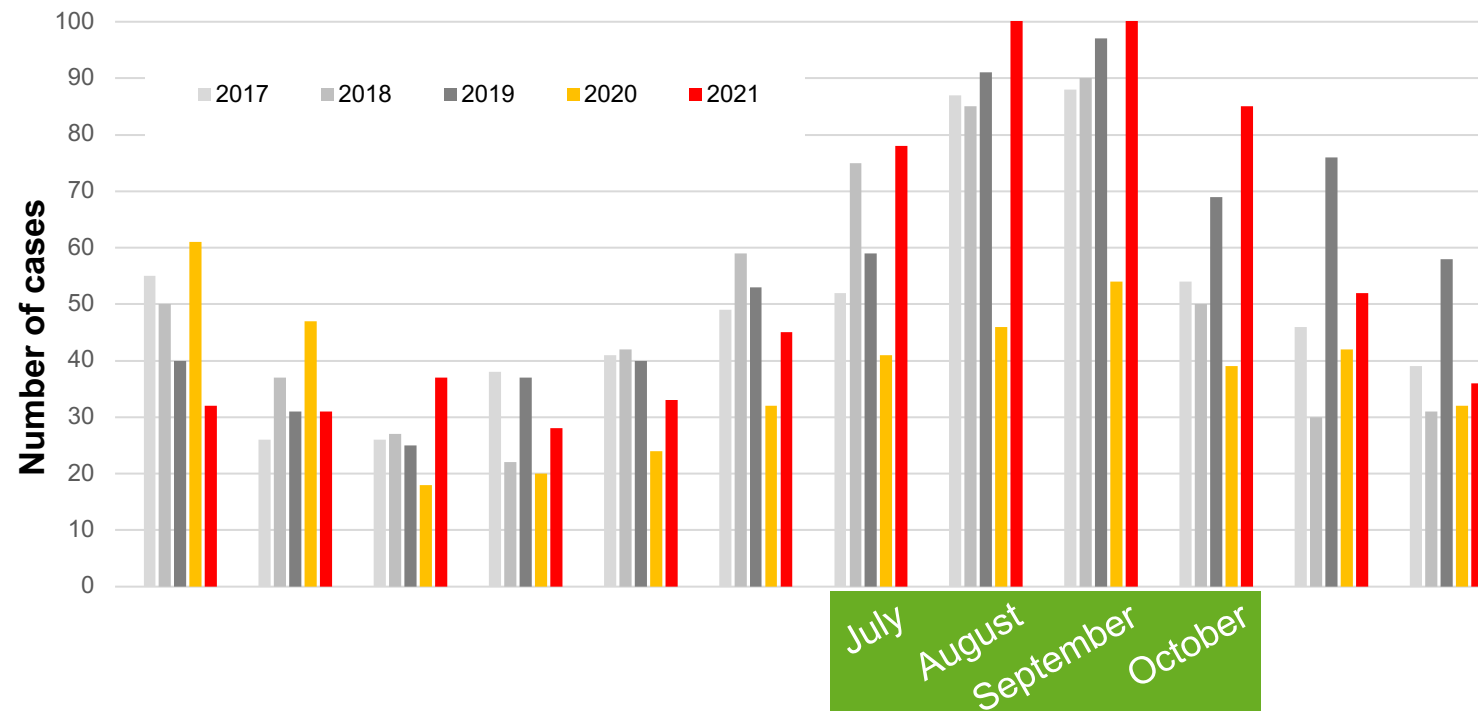
R Pijnacker<sup>1</sup>, MG Goris<sup>2</sup>, MJ te Wierik<sup>1</sup>, EM Broens<sup>3</sup>, JW van der Giessen<sup>14</sup>, M de Rosa<sup>15</sup>, JA Wagenaar<sup>34</sup>, RA Hartskeerl<sup>2</sup>, DW Notermans<sup>1</sup>, K Maassen<sup>1</sup>, B Schimmer<sup>1</sup>



Pijnacker *et al.* 2016

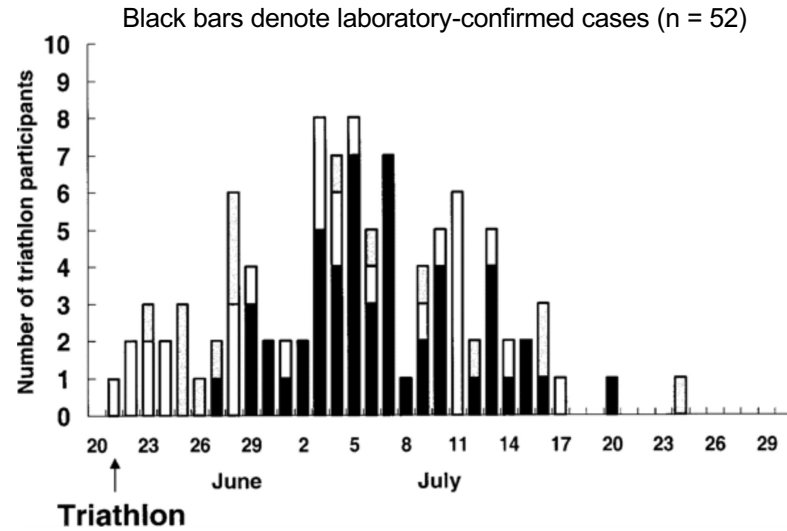
# Leptospirosis in Mainland France

Distribution of cases by month of the year



# Recreational exposure to water

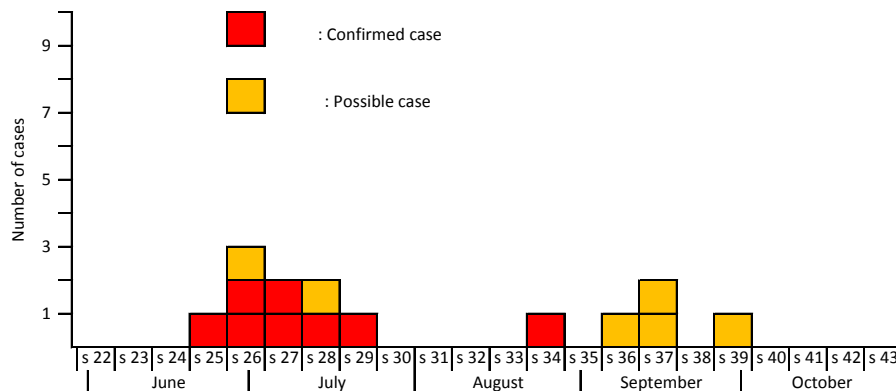
## Leptospirosis among triathlon participants in Springfield, IL



Participants in the Iron Horse Triathlon, Lake Springfield, IL

Morgan *et al.* 2002

## Leptospirosis among kayakers in Brittany, North-West France



Guillois *et al.* 2018

# Indirect contamination from the environment



Excretion of pathogenic *Leptospira* from the urine of animal reservoirs

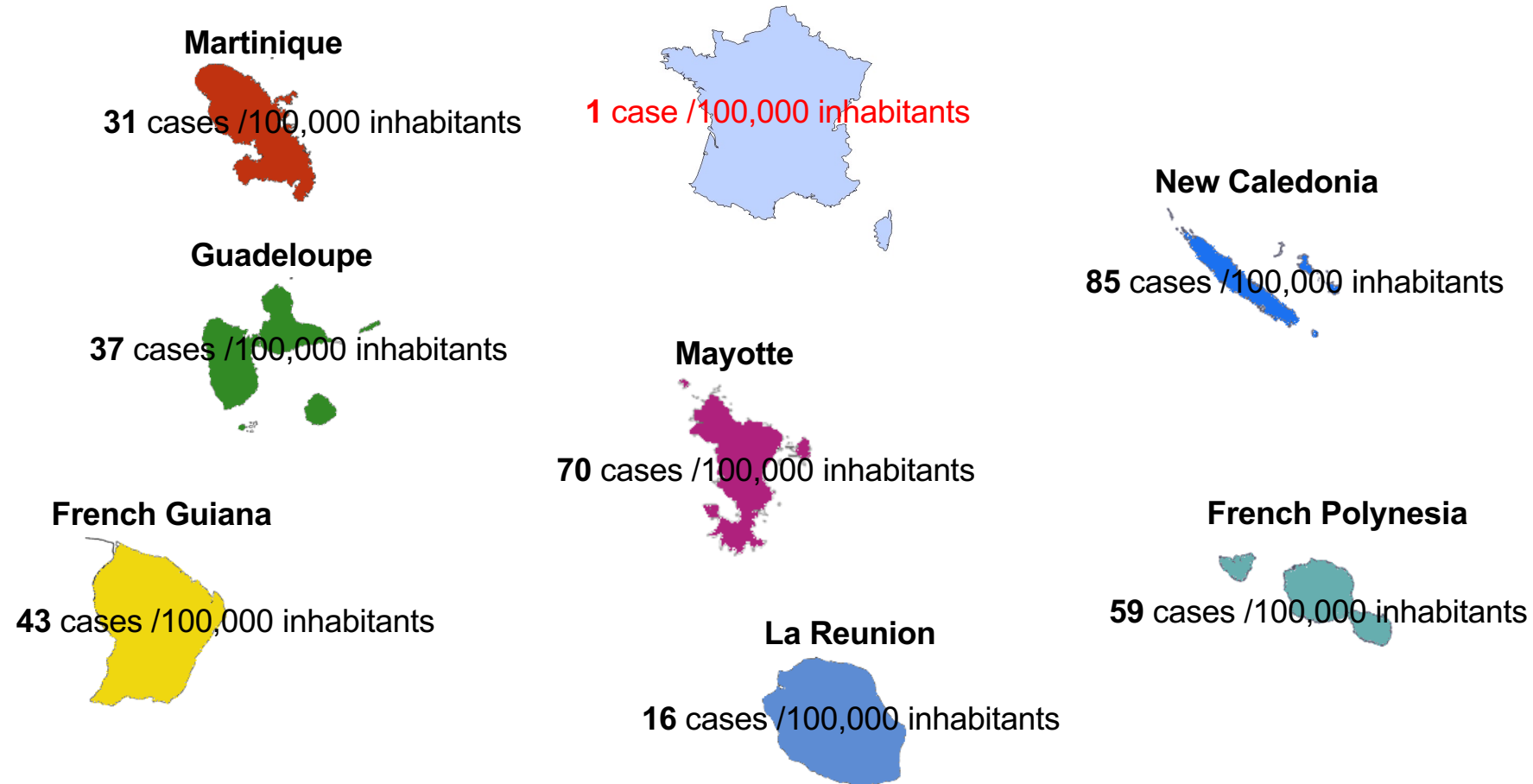


During heavy rainfall :  
- Resuspension of soil particles  
- Contamination of rivers, etc

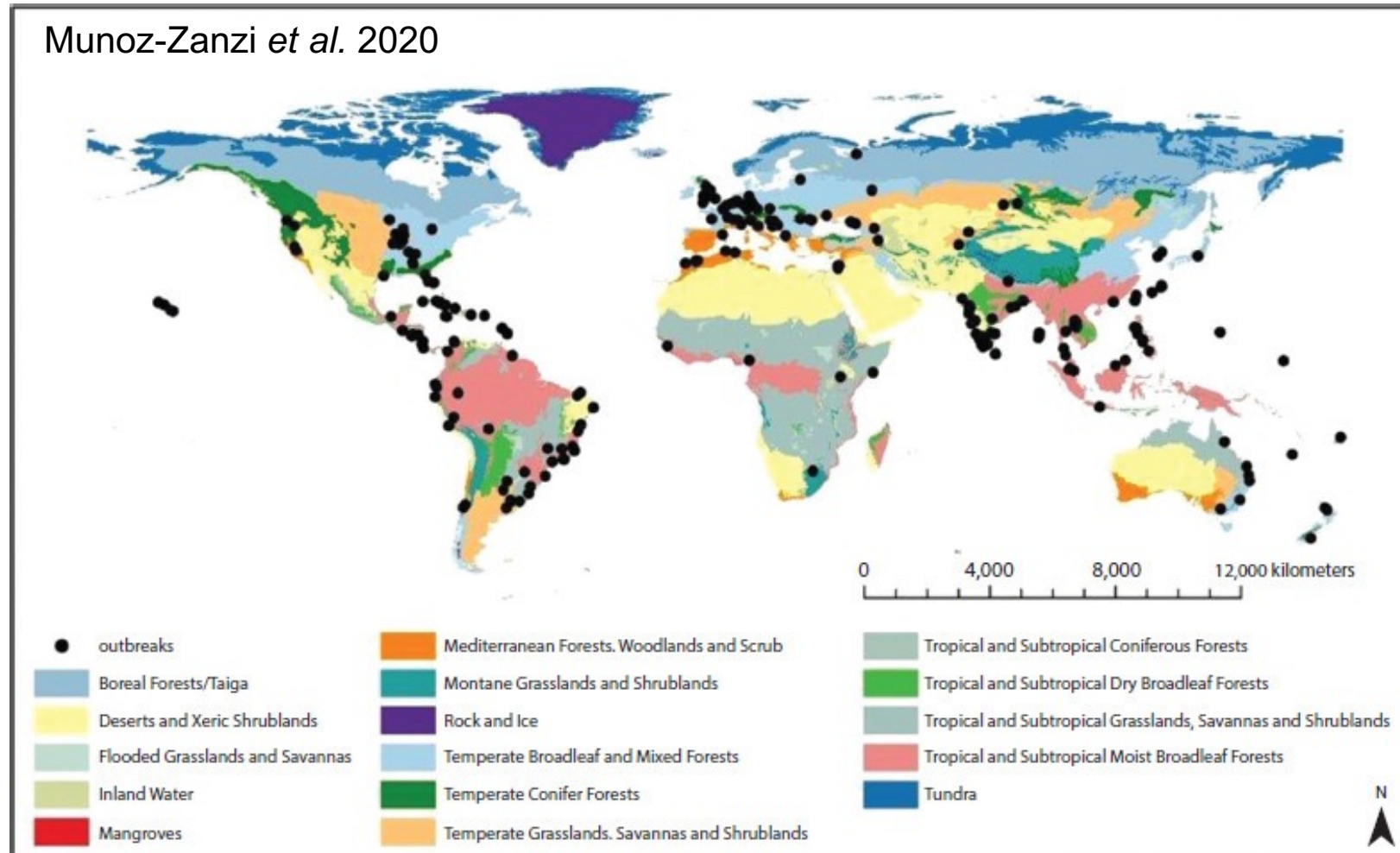


Survival of pathogenic *Leptospira*  
Exposure to contaminated water

# The incidence is much higher in french overseas territories in comparison to mainland France

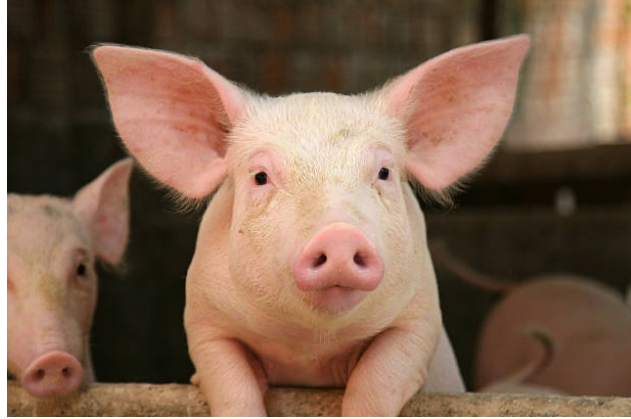


# Literature review of leptospirosis outbreaks worldwide, 1970–2012



Outbreaks (n=127):  
25% : work activities such as farming and agriculture  
23% : exposure to floodwaters due to increased rainfall, monsoon, or natural disasters  
22% : exposure to recreational swimming, water sports, or domestic use, e.g., bathing  
18% : not enough information to determine outbreak setting

# *Leptospira* infect a wide array of hosts



# In summary, leptospirosis is :

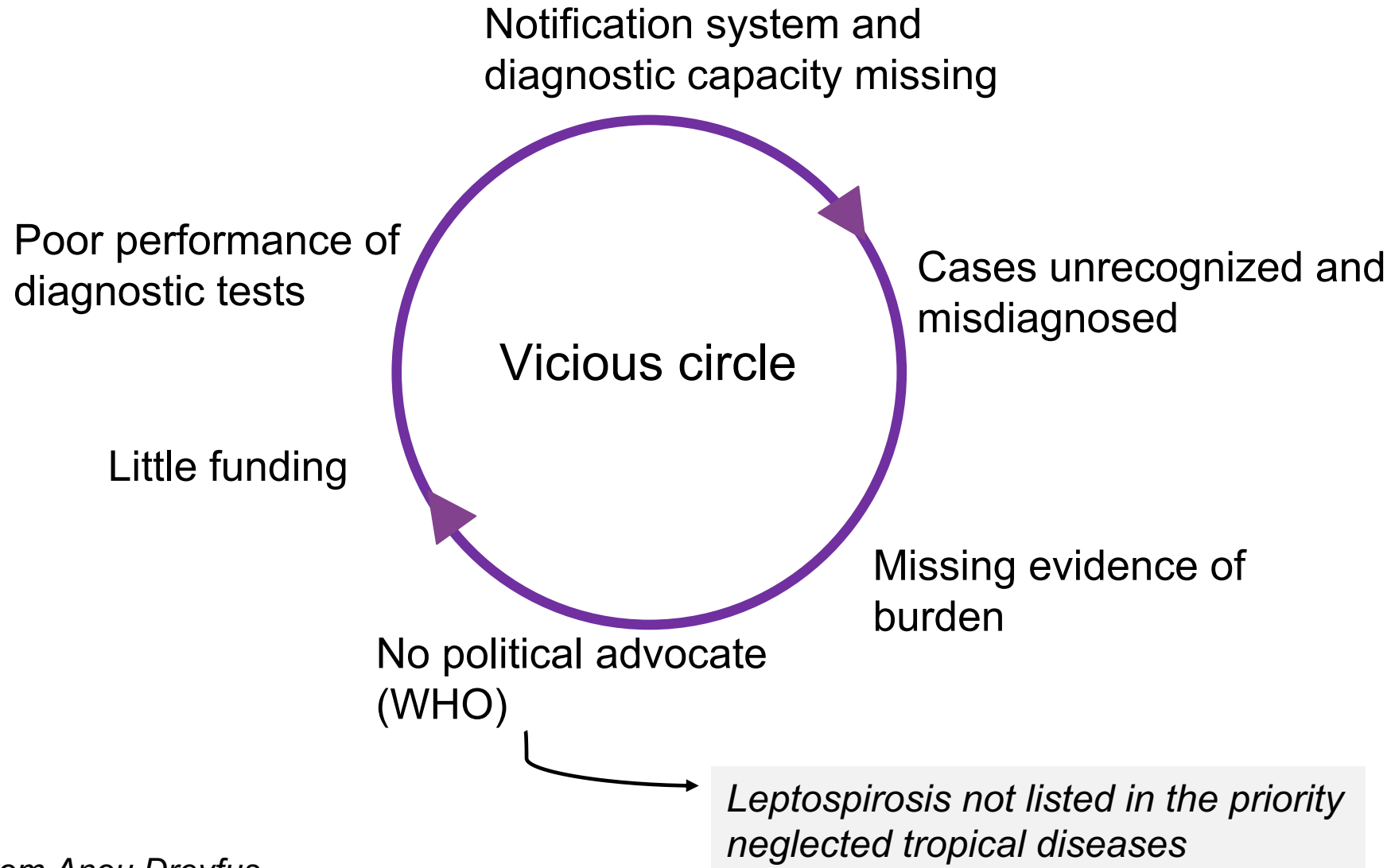
- A neglected disease
- A re-emerging disease (drivers for the re-emergence ?)
- A waterborne disease
- A **rodent-borne** and mammal-borne disease (economic loss due to leptospirosis in animals ?)
- A **urban** and rural disease
- A **tropical** and non-tropical disease
- An occupational and recreational disease
- Associated with natural disasters

# Neglected Tropical diseases

- >1 billion people around the world are affected
- Common in tropical countries
- Lack Public health attention at global and national level
- Mainly affect people living in poverty with inadequate access to clean water, basic sanitation and health care



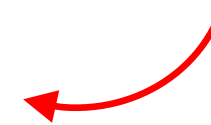
# The vicious circle of a neglected disease



## Neglected Tropical diseases prioritized by WHO

Category	Disease
Protozoan infections	1. Chagas disease 2. Human African trypanosomiasis 3. Leishmaniasis
Helminth infections	4. <i>Taenia solium</i> (neuro) cysticercosis/ Taeniosis 5. Dracunculiasis 6. Echinococcus 7. Foodborne trematodiasis 8. Lymphatic filariasis 9. Onchocerciasis 10. Schistosomiasis 11. Soil-transmitted helminthiasis (ascariasis, Hookworm diseases, trichuriasis, strongyloidiasis)
Bacterial infections	12. Buruli ulcer 13. Leprosy 14. Trachoma 15. Yaws
Viral infections	16. Dengue and chikungunya fevers 17. Rabies
Fungal Infections	18. Mycetoma, chromoblastomycosis, deep mycosis
Ectoparasitic infections	19. Scabies, Myiasis
Venom	20. Snakebite envenoming

Why not Leptospirosis ?

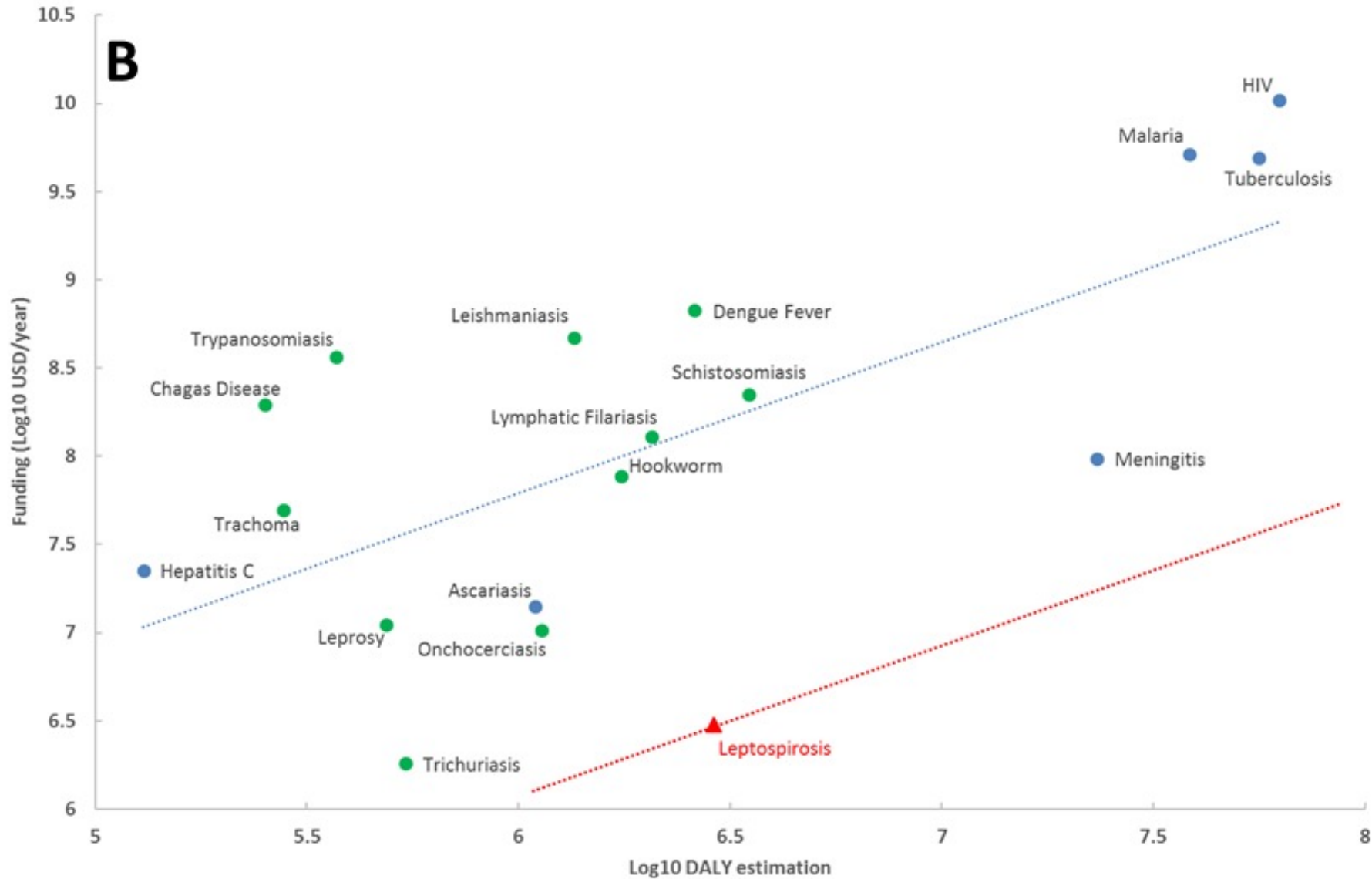


# The burden of malaria and neglected tropical diseases expressed in disability-adjusted life years (DALYs)

Diseases	DALYs per 100,000	Reference
Malaria	897.6 (728.1-1094.8)	Murray et al. 2015
Melioidosis	84 (57-120)	Birnie et al. 2019
Cholera	65 (49–84)	Murray et al. 1990
Leishmaniasis	58.6 (48.2-69.7)	Murray et al. 2015
Schistosomiasis	42.1 (23.3-77.8)	Murray et al. 2015
<b>Leptospirosis</b>	<b>42 (18.1-66)</b>	<b>Torgerson et al. 201</b>
Lymphatic filariasis	28.9 (15.7-47.1)	Murray et al. 2015 [65]
Rabies	17.3 (12.7-21.2)	Murray et al. 2015 [65]
Dengue	15.8 (10.1-27.4)	Murray et al. 2015 [65]

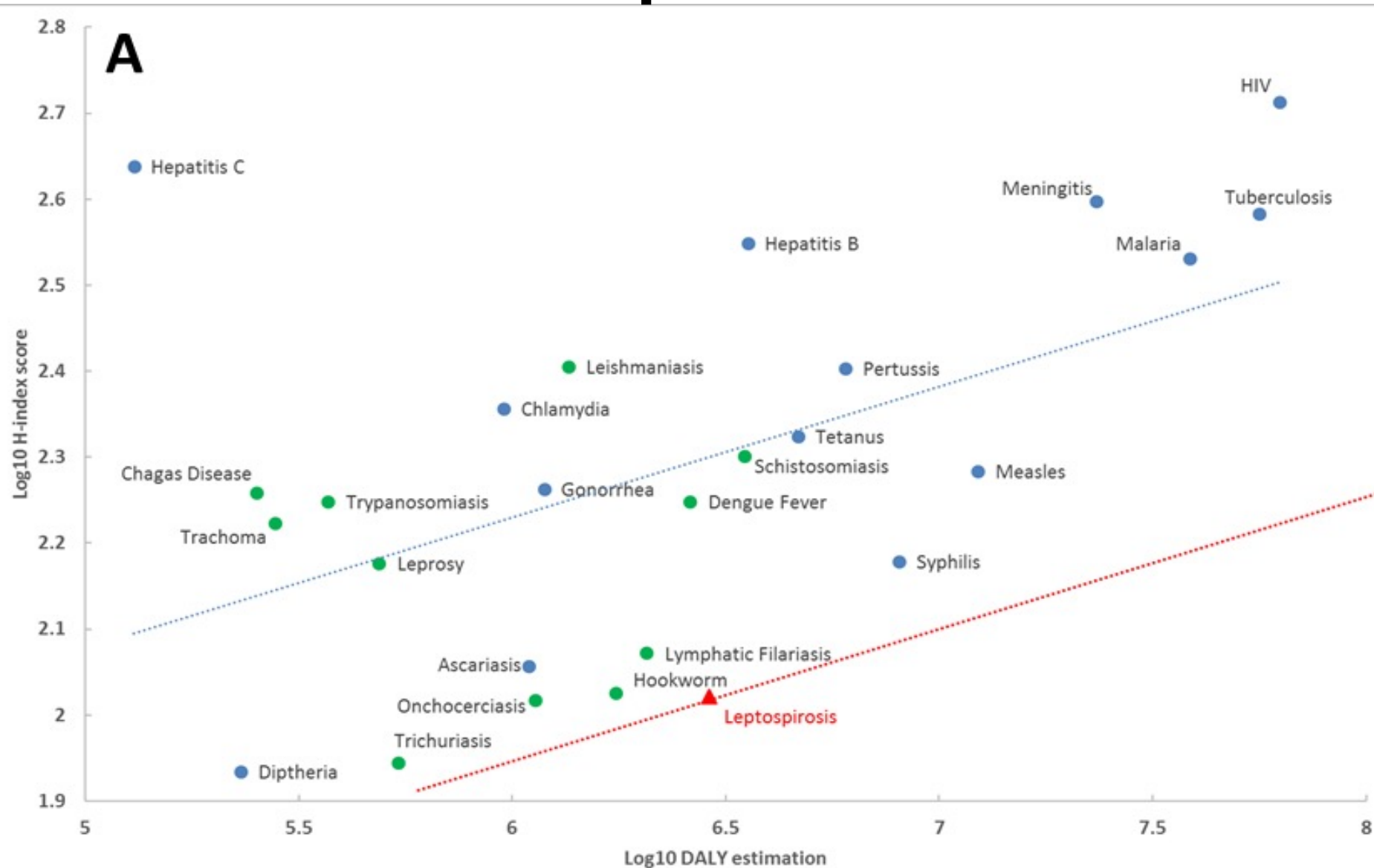
Goarant *et al.* 2021

# Relationship between the global burden of disease and research funding



Goarant *et al.* 2019

# Relationship between the global burden of disease and relative research impact

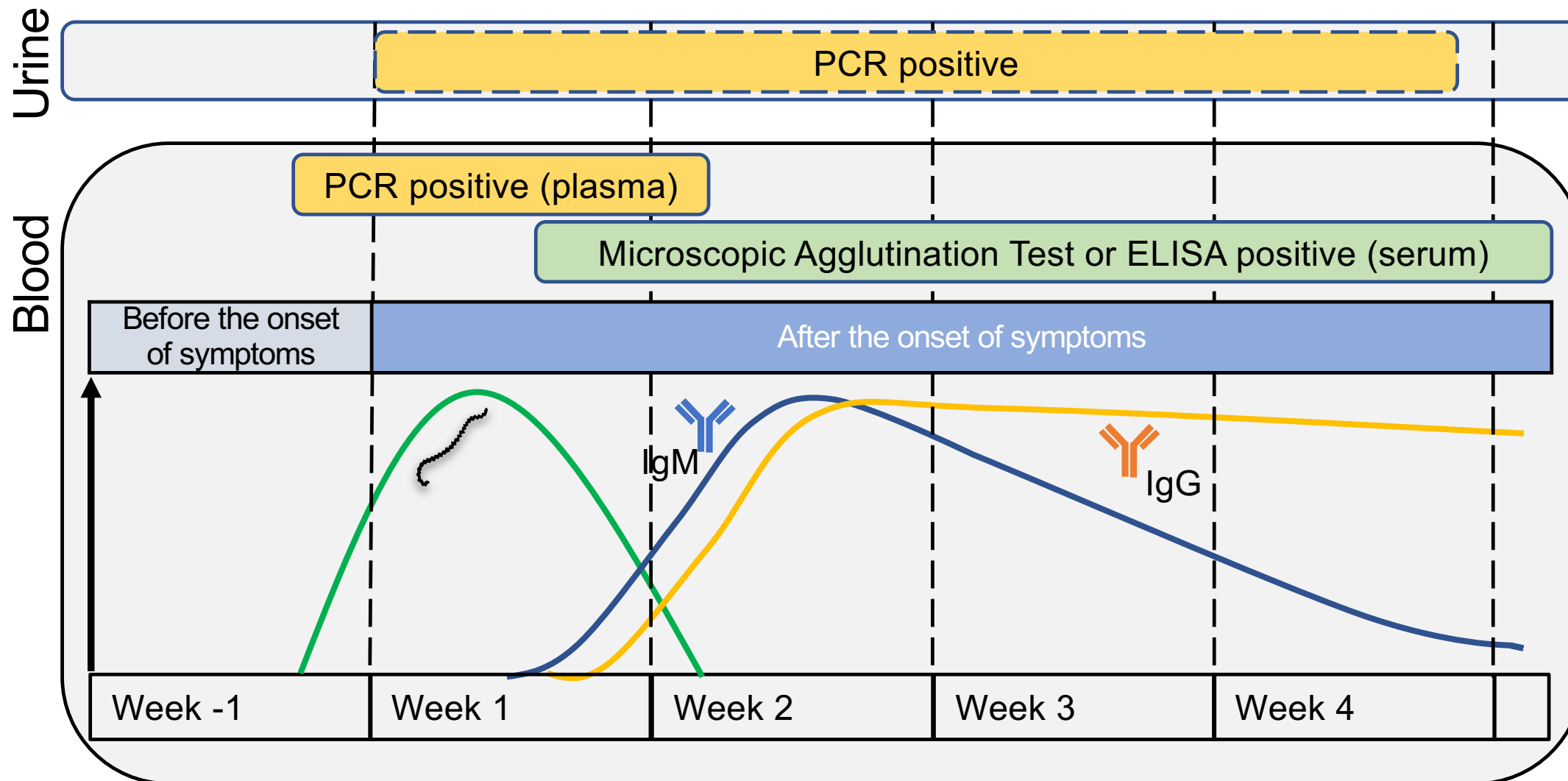


Goarant *et al.* 2019

# Diagnosis

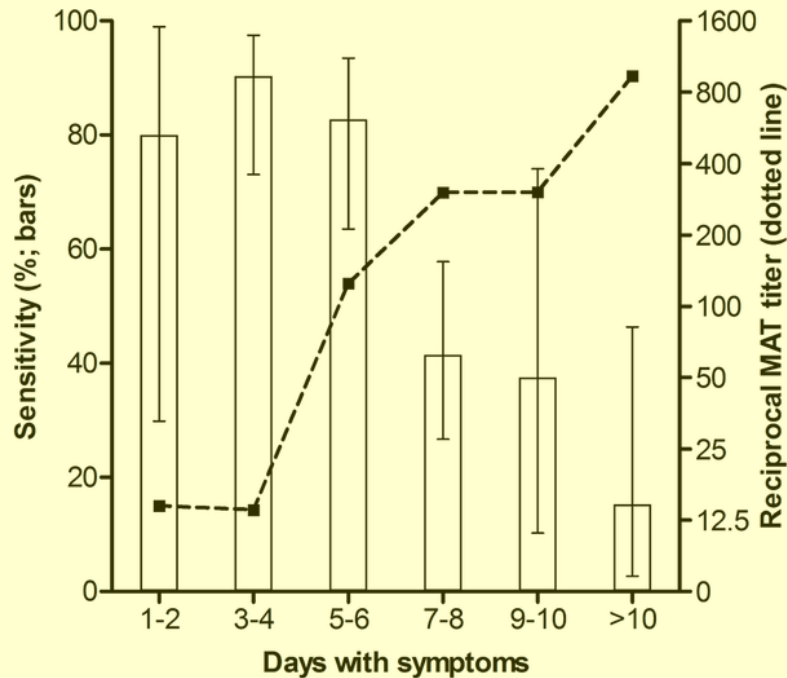
- Clinical presentations:
  - Acute undifferentiated fever with possible headache, muscle pain, chills, jaundice, renal failure
  - Misdiagnosis common (malaria, dengue, etc)
- Low sensitivity of diagnostic tests:
  - PCR (blood, urine)
  - Serology (IgM ELISA, Microscopic Agglutination Test)

# Kinetics of leptospirosis and diagnosis



# Real-time PCR assay on blood for early diagnosis of leptospirosis

Positivity of the real-time PCR assay according to days after onset of symptoms



- Target genes: *lipL32*, *secY*, *lfb1*, etc
- Higher sensitivity for blood samples from the first week after the onset of symptoms
- Higher sensitivity on plasma in comparison to serum
- *Leptospira* may be shed intermittently in the urine during the infection
- Antibiotherapy may lead to negative results

# IgM ELISA

- Highly variable performance of the kits according to the local epidemiology
- Some serovars (Australis and Grippotyphosa) are not well-detected
- Early detection in comparison to MAT

Sensitivities of three serological tests assays according to DPO (using qPCR as gold) :

Number of patients	DPO	ELISA Serion	ELISA Pasteur-Hb	GenBio Immunodot
n=40	0-5	<b>32</b> (22-50)	<b>30</b> (18-45)	<b>42</b> (29-58)
		p<0.05	p<0.05	NS
n=21	6-10	<b>86</b> (65-95)	<b>76</b> (55-89)	<b>67</b> (45-83)
		NS	NS	NS
n=16	11-15	<b>94</b> (72-99)	<b>93</b> (72-99)	<b>94</b> (72-99)
		NS	NS	NS
n=26	>15	<b>92</b> (75-98)	<b>96</b> (80-99)	<b>92</b> (75-98)
		NS	NS	NS

Significantly different results between two consecutive DPO intervals are indicated by p<0.05

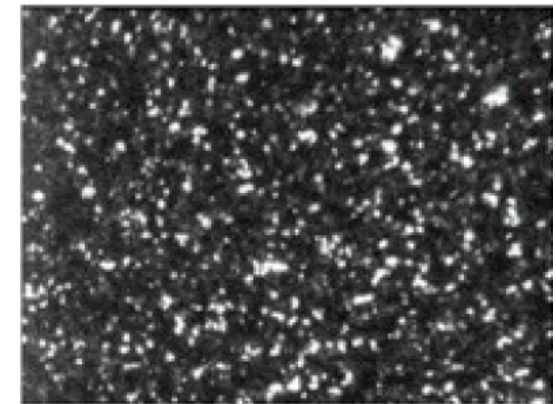
# Microscopic Agglutination test / MAT

- Reference test for the serodiagnosis of leptospirosis
- Living antigens (cultures of locally representative serovars)
- Evaluation of the degree of agglutination between each antigen and dilutions of the patient serum
- Use of paired samples greatly improves case confirmation
  
- Can give informations on the infecting serogroup but not always a good predictor :
  - Anti-*Leptospira* antibodies show a high degree of cross-reactivity
  - Paradoxical MAT reactions
  - Variability in MAT titers across laboratories

Dark-field microscopy



Negative Control



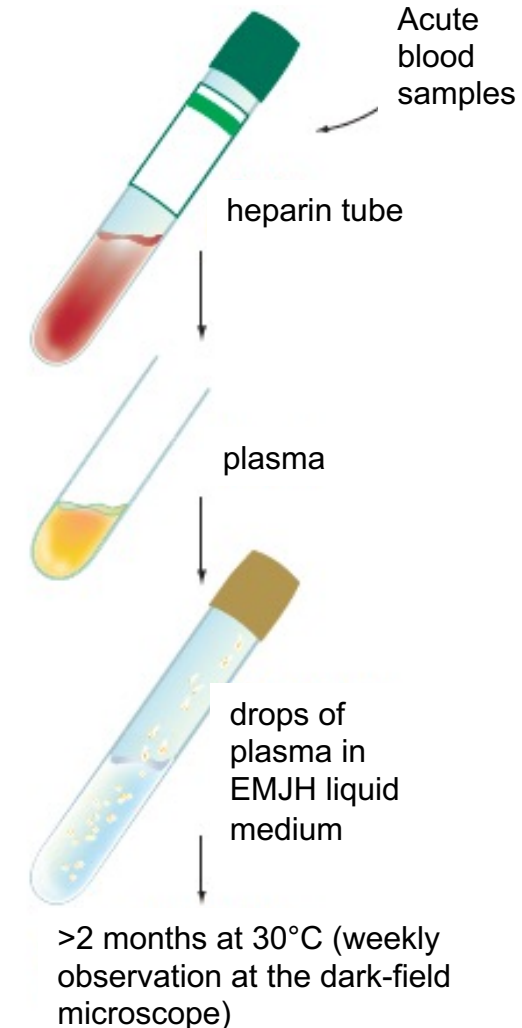
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# Reference strains used as antigens for MAT

Ag	Species	Serogroup	Serovar	Strain
1	<i>L. interrogans</i>	Australis	Australis	Ballico
2	<i>L. interrogans</i>	Autumnalis	Autumnalis	Akiyami A
3	<i>L. interrogans</i>	Bataviae	Bataviae	Van Tienen
4	<i>L. interrogans</i>	Canicola	Canicola	Hond Utrecht IV
5	<i>L. borgpetersenii</i>	Ballum	Castellonis	Castellon 3
6	<i>L. kirschneri</i>	Cynopteri	Cynopteri	3522 C
7	<i>L. kirschneri</i>	Grippotyphosa	Grippotyphosa	Moskva V
8	<i>L. interrogans</i>	Sejroe	Hardjobovis	Sponselee
9	<i>L. interrogans</i>	Hebdomadis	Hebdomadis	Hebdomadis
10	<i>L. interrogans</i>	Icterohaemorrhagiae	Copenhageni	Wijnberg
11	<i>L. noguchii</i>	Panama	Panama	CZ 214 K
12	<i>L. biflexa</i>	Semaranga	Patoc	Patoc 1
13	<i>L. interrogans</i>	Pomona	Pomona	Pomona
14	<i>L. interrogans</i>	Pyrogenes	Pyrogenes	Salinem
15	<i>L. borgpetersenii</i>	Sejroë	Sejroë	M 84
16	<i>L. borgpetersenii</i>	Tarassovi	Tarassovi	Mitis Johnson
17	<i>L. interrogans</i>	Icterohaemorrhagiae	Icterohaemorrhagiae	Verdun
18	<i>L. weilii</i>	Celledoni	ND	2011/01963
19	<i>L. interrogans</i>	Djasiman	Djasiman	Djasiman
20	<i>L. borgpetersenii</i>	Mini	ND	2008/01925
21	<i>L. weilii</i>	Sarmin	Sarmin	Sarmin
22	<i>L. santarosai</i>	Shermani	Shermani	1342 K
23	<i>L. borgpetersenii</i>	Javanica	Javanica	Poi
24	<i>L. noguchii</i>	Louisiana	Louisiana	LUC1945

# Culture isolation

- Challenging and fastidious
- Isolation from blood or urine before ATB treatment
- Frequent contamination
- *Leptospira* are slow-growing bacteria (>1 month for pathogens)
- No diagnostic value but epidemiological value (identification at the species / serogroup levels)



# In summary, which assay and which sample to use according to the kinetics of infection ?

	≤10 days post onset symptoms	≥10 days post onset symptoms
PCR plasma	yes	
PCR urine	yes	yes
IgM ELISA serum	yes	yes
MAT serum		yes

# Challenges for Diagnosis

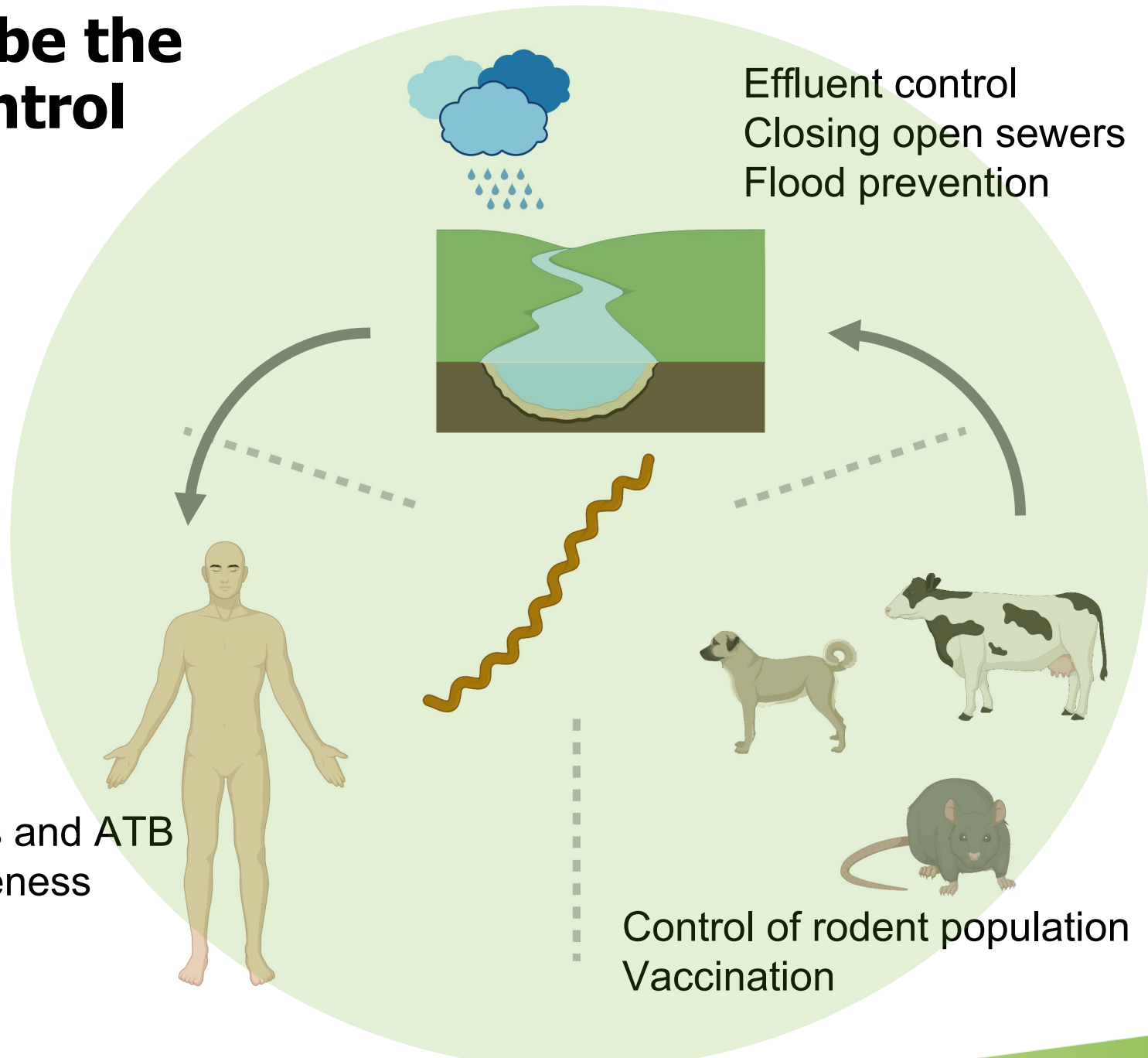
- Leptospirosis has varied clinical presentations
- Contact with animals or water exposure (flooding, etc)
- Testing is imperfect
  - Negative PCR does not rule out leptospirosis; window of opportunity is narrow in blood and excretion in urine not constant
  - Highly variable performance of the IgM ELISA kits (positive threshold value must be re-evaluated)
  - Use of MAT to confirm positive IgM ELISA
    - MAT is performed by few reference laboratories (require well-trained personnel, etc)
- Diagnostics complicated by large heterogeneity of agents

# What could be the effective control measures ?

## Risk factors :

- Jobs at high risks: people who work outdoors or with animals, such as rice and sugar-cane field workers, farmers, sewer workers, abattoir workers, etc
- Recreational exposure: water sports, etc
- Natural disasters: flooding, heavy rainfalls, hurricanes, etc  
Mostly in tropical countries

# What could be the effective control measures ?



# Preventive and control measures

- Complex prevention (environment, animal reservoir, humans, diversity of leptospires, etc)
- Vaccination in human (Spirolept: D0-J15-M6, booster every 2 years) and animals (cattle, dogs, etc)
- Personal protection (gloves, boots, waterproof dressing, etc)
- Closure of open sewers, effluent control (industrial livestock farms)
- Controlling the proliferation of reservoirs (waste management, etc)
- Early diagnosis and antibiotic treatment



# Antibiotics for leptospirosis

- Treatment is most effective when started as soon as possible
  - Mild leptospirosis : oral agents such as doxycycline or amoxicillin
  - Severe leptospirosis : intravenous penicillin or cephalosporins of third generation
- Data on antimicrobial susceptibilities of *Leptospira* isolates are scarce
- No antibiotic resistant strains reported in clinical isolates

# Antibiotics for leptospirosis

[Intervention Review]

## Antibiotics for treatment of leptospirosis

Tin Zar Win<sup>1</sup>, Su Myat Han<sup>1,2</sup>, Tansy Edwards<sup>3</sup>, Hsu Thinzar Maung<sup>1</sup>, David M Brett-Major<sup>4</sup>, Chris Smith<sup>1,5</sup>, Nathaniel Lee<sup>2,6</sup>

<sup>1</sup>School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan. <sup>2</sup>Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK. <sup>3</sup>Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, UK. <sup>4</sup>Department of Preventive Medicine and Biometrics, Uniformed Services University, Bethesda, Maryland, USA. <sup>5</sup>Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London, UK. <sup>6</sup>School of Tropical Medicine and Global Health, Nagasaki University, Nagasaki, Japan

**Contact:** Chris Smith, [christopher.smith@lshtm.ac.uk](mailto:christopher.smith@lshtm.ac.uk).

**Editorial group:** Cochrane Hepato-Biliary Group.

**Publication status and date:** New, published in Issue 3, 2024.

**Citation:** Win TZ, Han SM, Edwards T, Maung HT, Brett-Major DM, Smith C, Lee N. Antibiotics for treatment of leptospirosis. *Cochrane Database of Systematic Reviews* 2024, Issue 3. Art. No.: CD014960. DOI: [10.1002/14651858.CD014960.pub2](https://doi.org/10.1002/14651858.CD014960.pub2).

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We do not know if antibiotics provide little to no effect on all-cause mortality... There is a lack of definitive rigorous data from randomised trials to support the use of antibiotics for treating leptospirosis infection.

[Intervention Review]

## Antibiotic prophylaxis for leptospirosis

Tin Zar Win<sup>1</sup>, Tanaraj Perinpanathan<sup>1,2</sup>, Patrick Mukadi<sup>3,4,5</sup>, Chris Smith<sup>1,2</sup>, Tansy Edwards<sup>6</sup>, Su Myat Han<sup>1,6</sup>, Hsu Thinzar Maung<sup>1</sup>, David M Brett-Major<sup>7</sup>, Nathaniel Lee<sup>1,6</sup>

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**Contact:** Chris Smith, [christopher.smith@lshtm.ac.uk](mailto:christopher.smith@lshtm.ac.uk).

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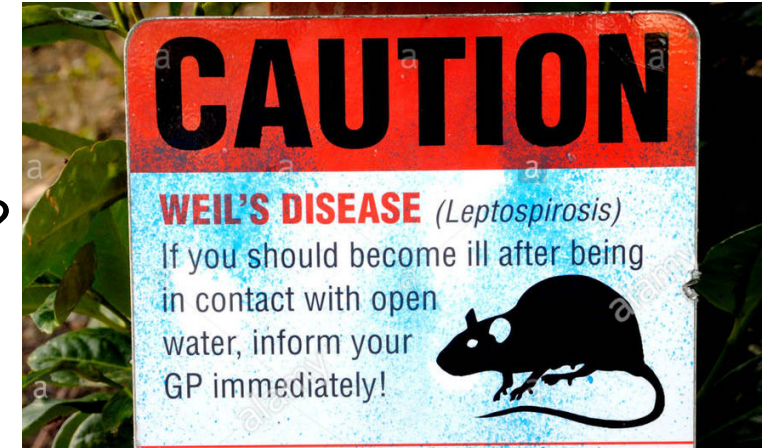
We lack definitive rigorous data from randomised trials to support the use of antibiotics for the prophylaxis of leptospirosis infection. We lack trials reporting data on clinically relevant outcomes

# Leptospirosis and the Environment

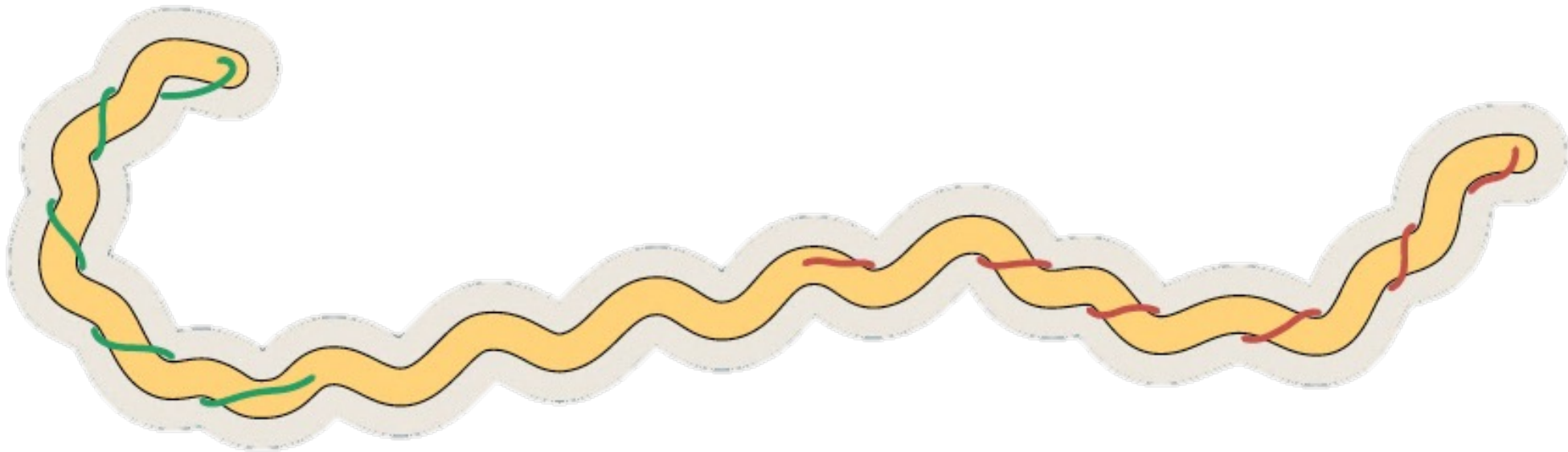
- *Leptospira* are not used as indicators of water quality

*What should be done if pathogenic leptospirae are detected? Closure to bathing? Conditions for reopening?*

- What are the factors favouring the survival of bacteria?
- Are pathogens capable of multiplying in the environment ?
- Antibiotic prophylaxis in the event of flooding
- Raising awareness of the risks involved (education programme, prediction models, etc)

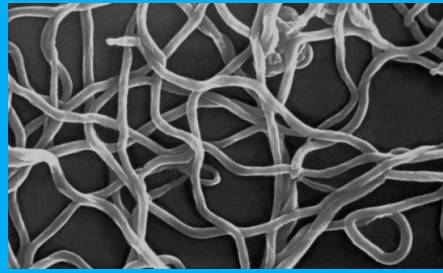


# *Leptospira*



# Spirochaetes are causing major animal and human diseases

## *Borrelia burgdorferi*



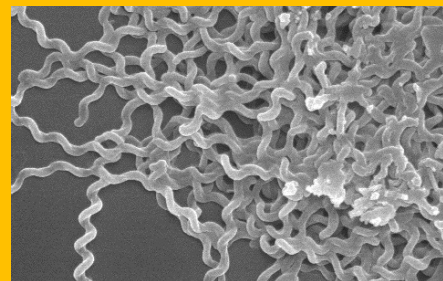
**Lyme disease**  
**300,000 cases/year in the US**  
**90,000 cases/year in Europe**  
(>30,000 in France)  
**Fatality rate <1%**

## *Treponema pallidum*



**Syphilis**  
**6 million cases /year**  
(1000 cases/year in France)  
**Fatality rate <1%**

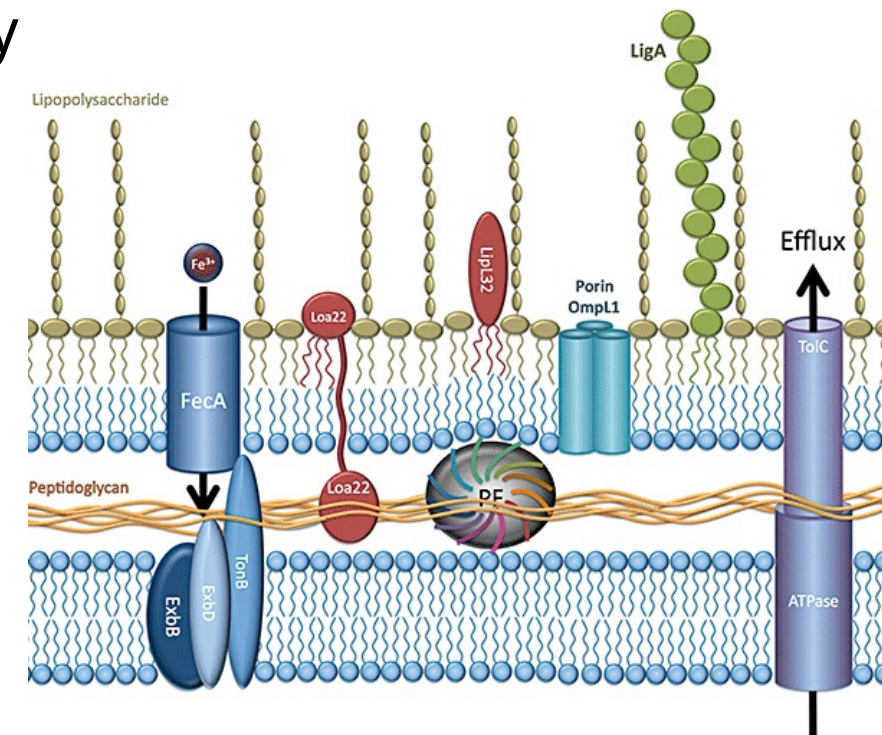
## *Leptospira interrogans*



**Leptospirosis**  
**1 million cases/year**  
(700 cases in France)  
**Fatality rate >10%**

# *Leptospira*, a pathogen without classical virulence factors ?

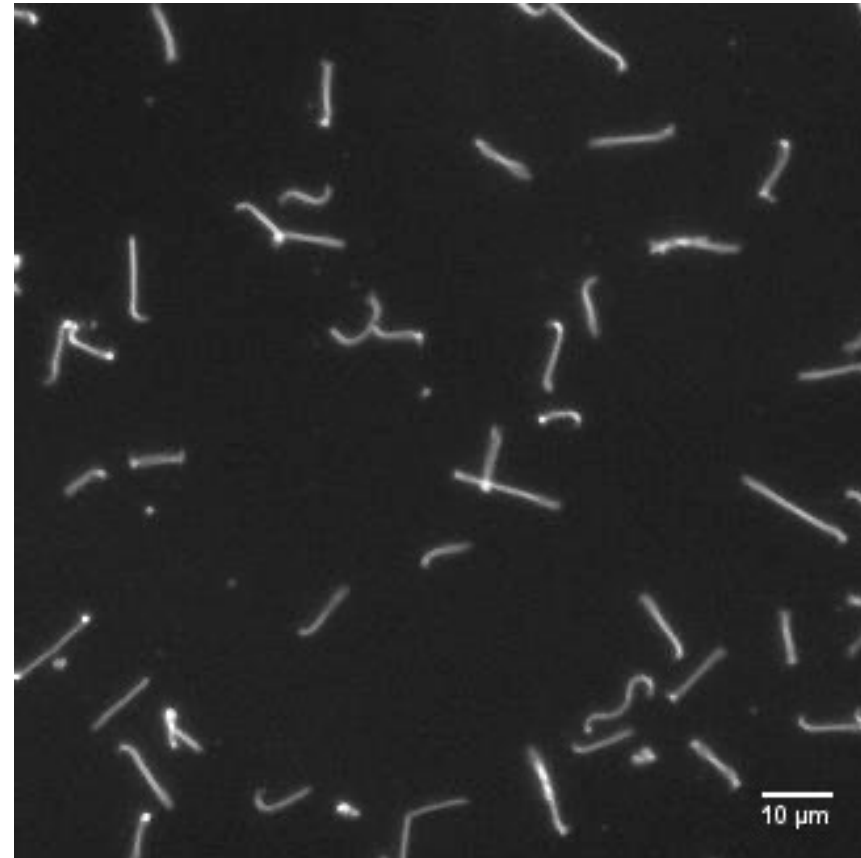
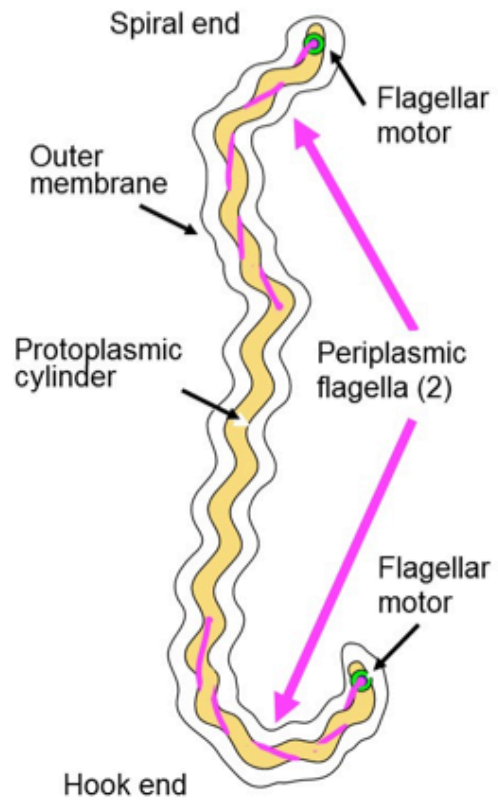
- Extracellular bacteria
- Stealth pathogens (evasion of the complement system and recognition by the innate immune cells)
- Surface-exposed LPS; atypical lipid A with low toxicity
- No type III to type X secretions systems
- No pathogenicity islands or virulence plasmids
- Endoflagellar system
- Over-representation of genes of unknown function



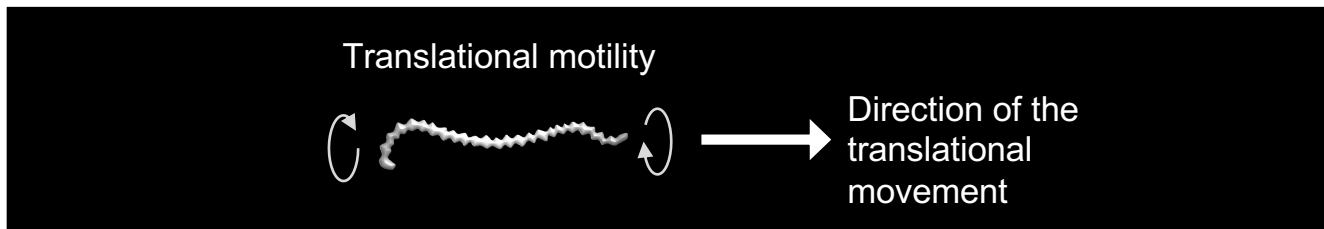
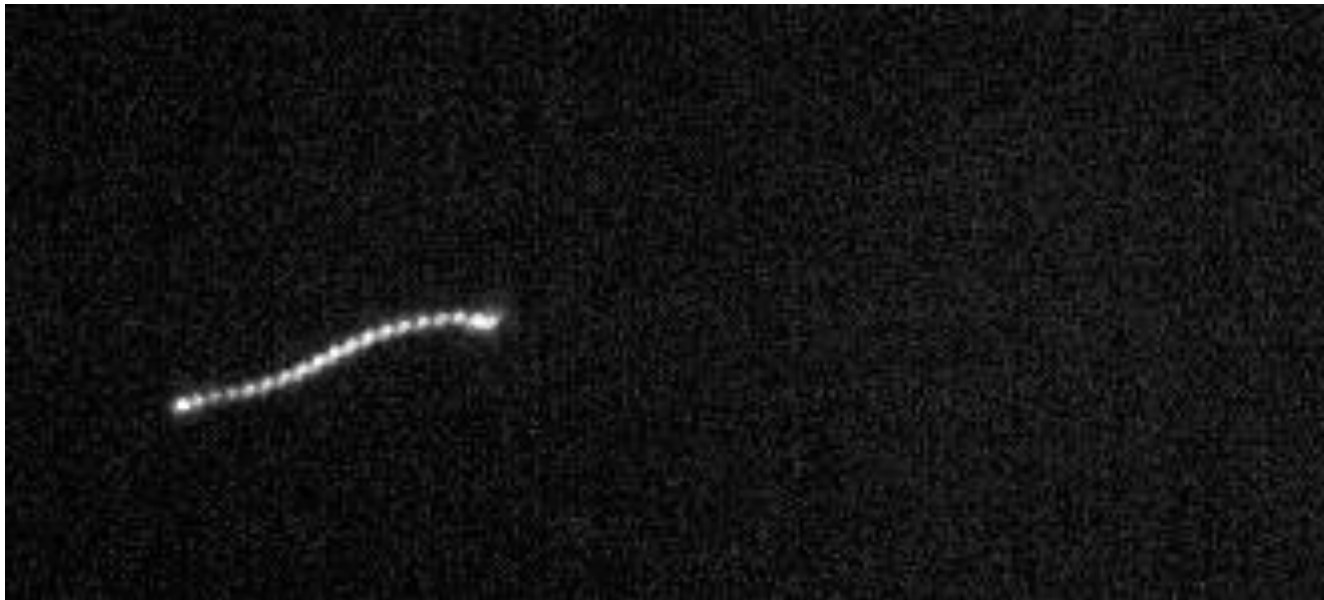
Haake *et al.* 2010

# What does the agent of leptospirosis look like ?

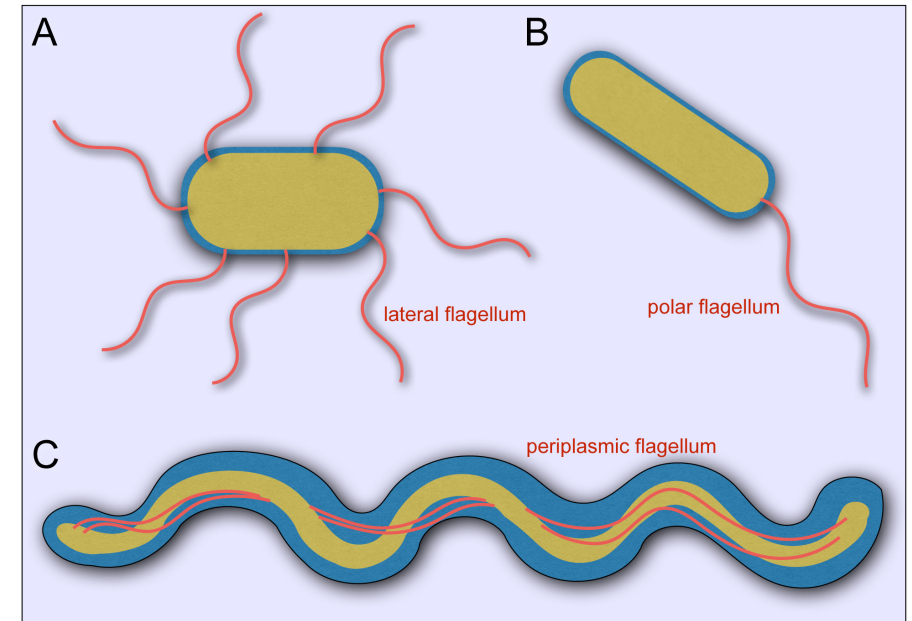
- Long, thin spiral-shaped and motile bacteria



# A bacteria with corkscrew motility



## Bacterial flagella

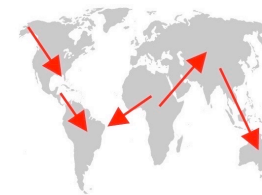
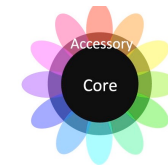
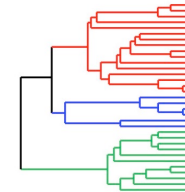


# Whole-genome sequencing of *Leptospira*

Gene content and genome organization

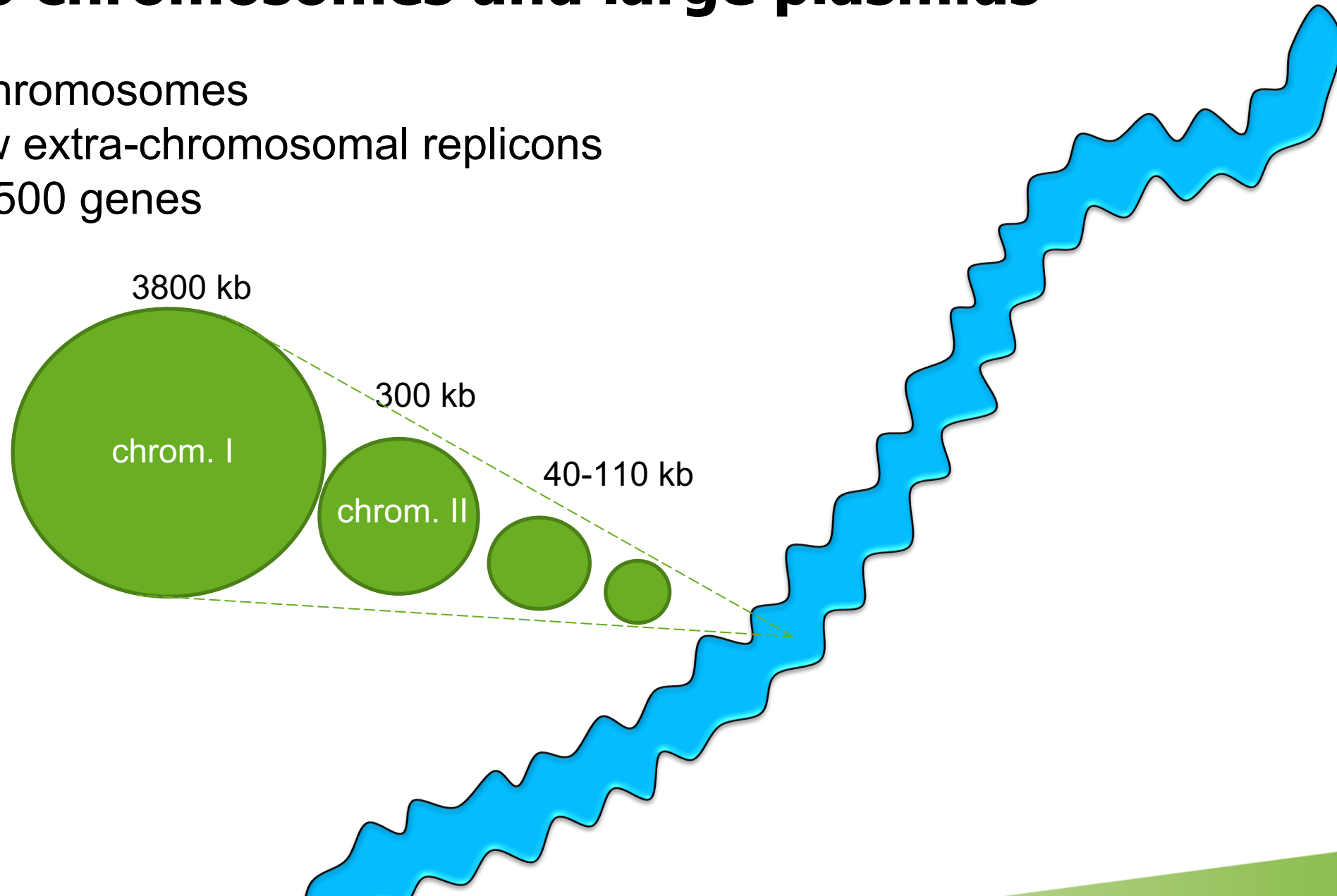
Comparative genomics:

- Phylogenetic tree (diversity)
- Pangenome analysis
- Global mapping of circulating strains
- Virulence evolution



# Two chromosomes and large plasmids

- 2 chromosomes
- new extra-chromosomal replicons
- >3,500 genes



# ***Leptospira* diversity**

Why taxonomic description / typing is important ?

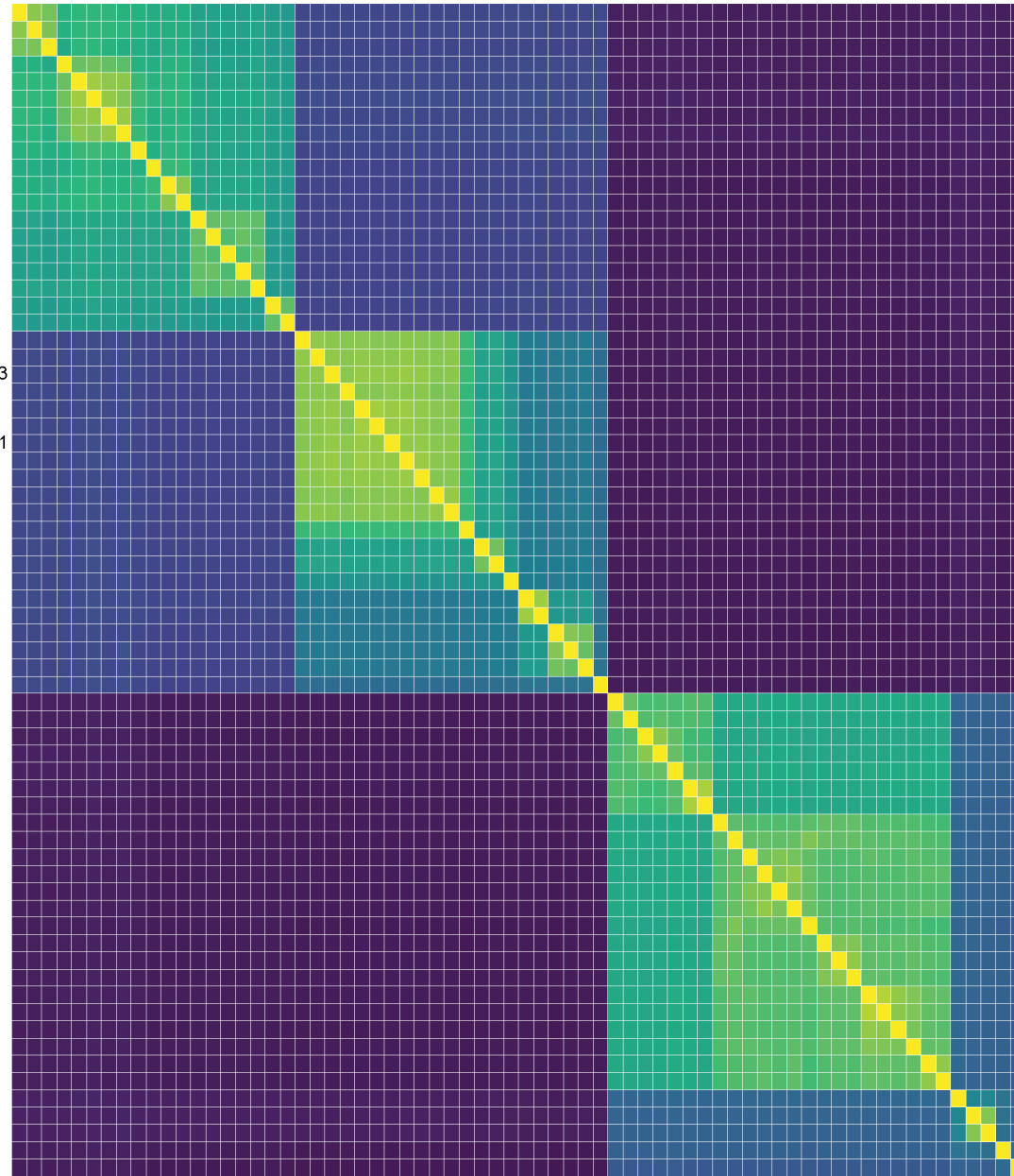
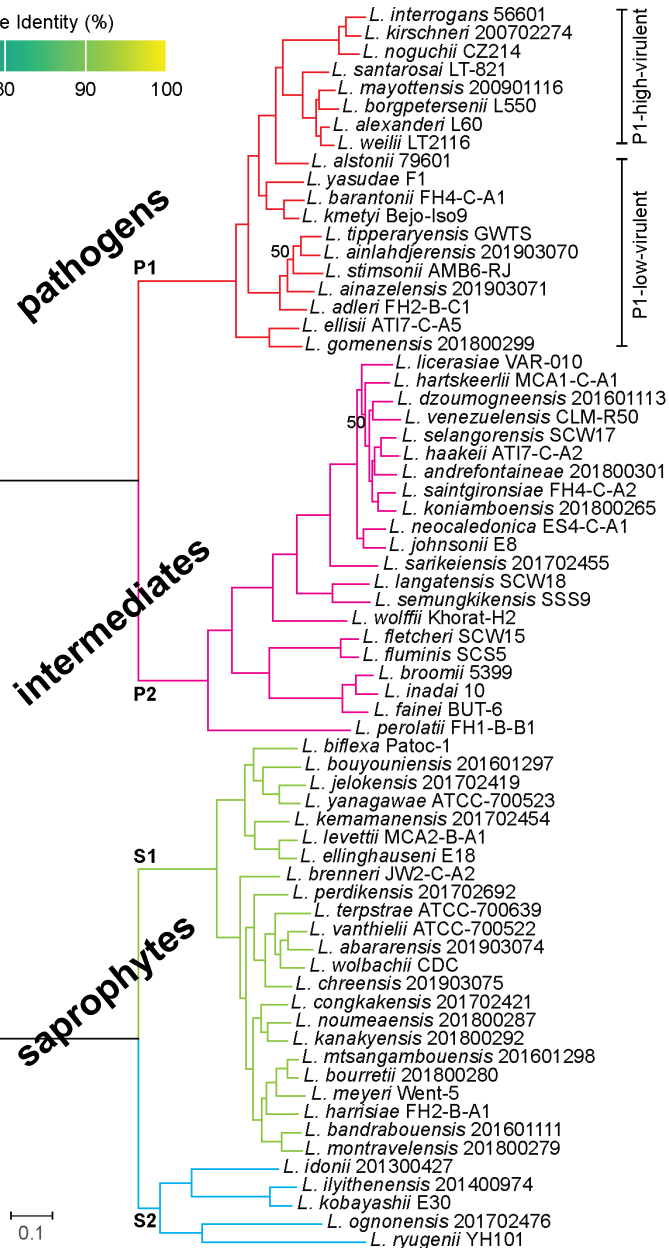
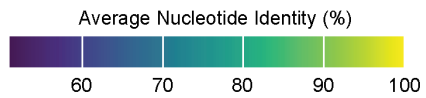
At the species (and serogroup/serovar) level:

**i) Official recognition**

**ii) Common language** for communicating scientific results

**iii) Accurate description** of microbial **diversity** (diagnosis, vaccines, epidemiology, tracking emergence of clones, etc)

# Leptospira is a genus of 69 species and 4 subclades

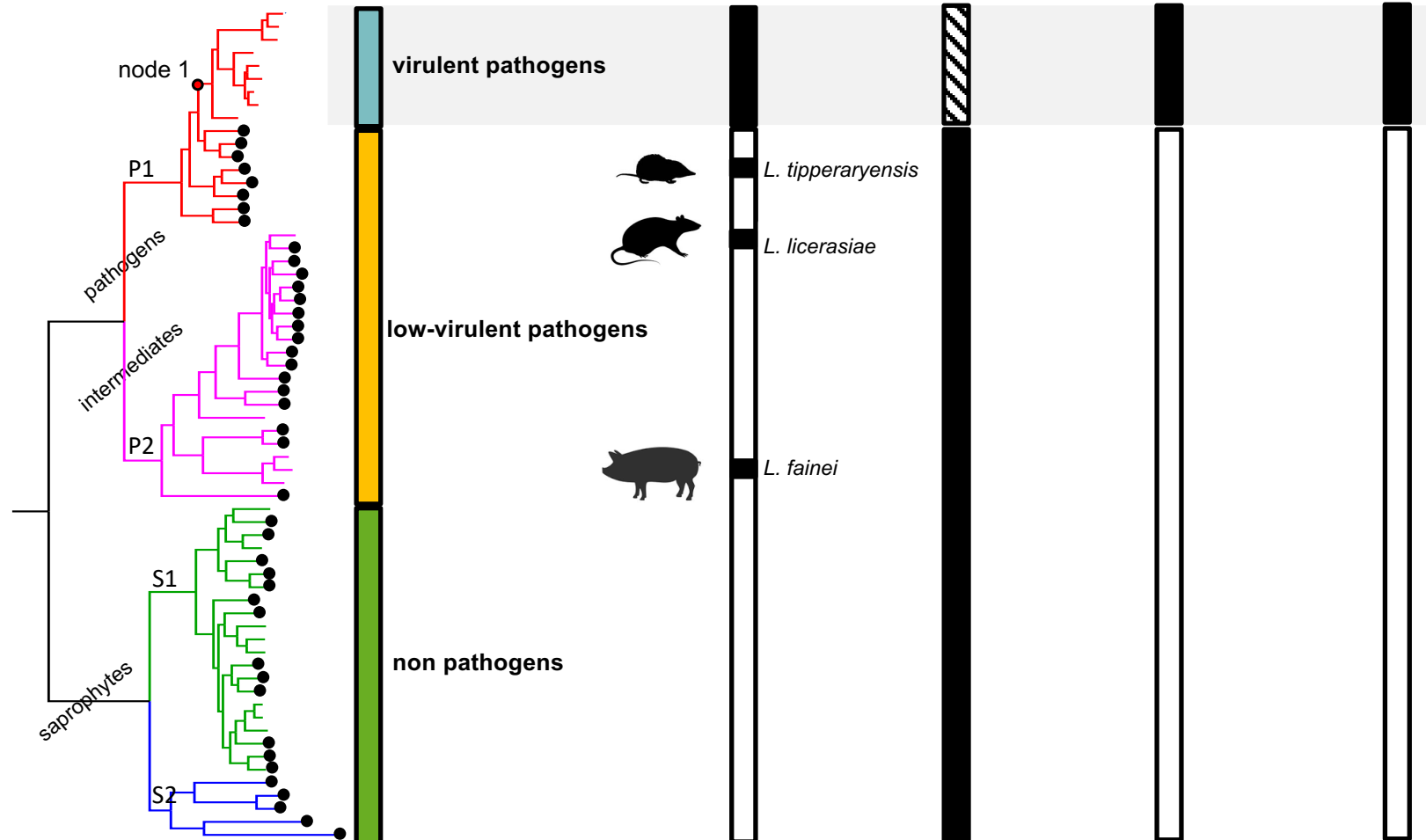




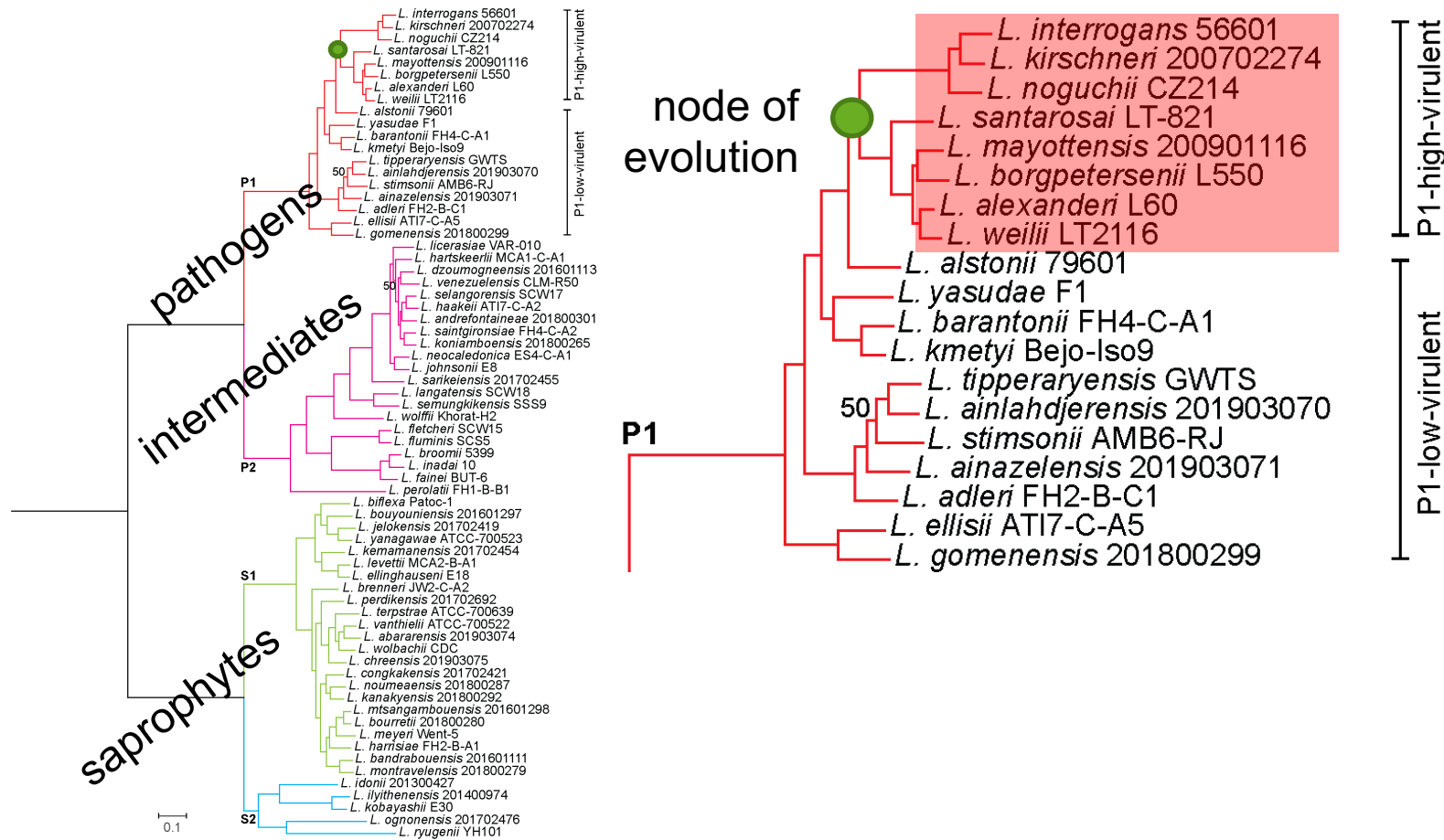
Isolation from patients/animals  
Isolation from environment  
Infection and/or colonization  
in animal models



● New species

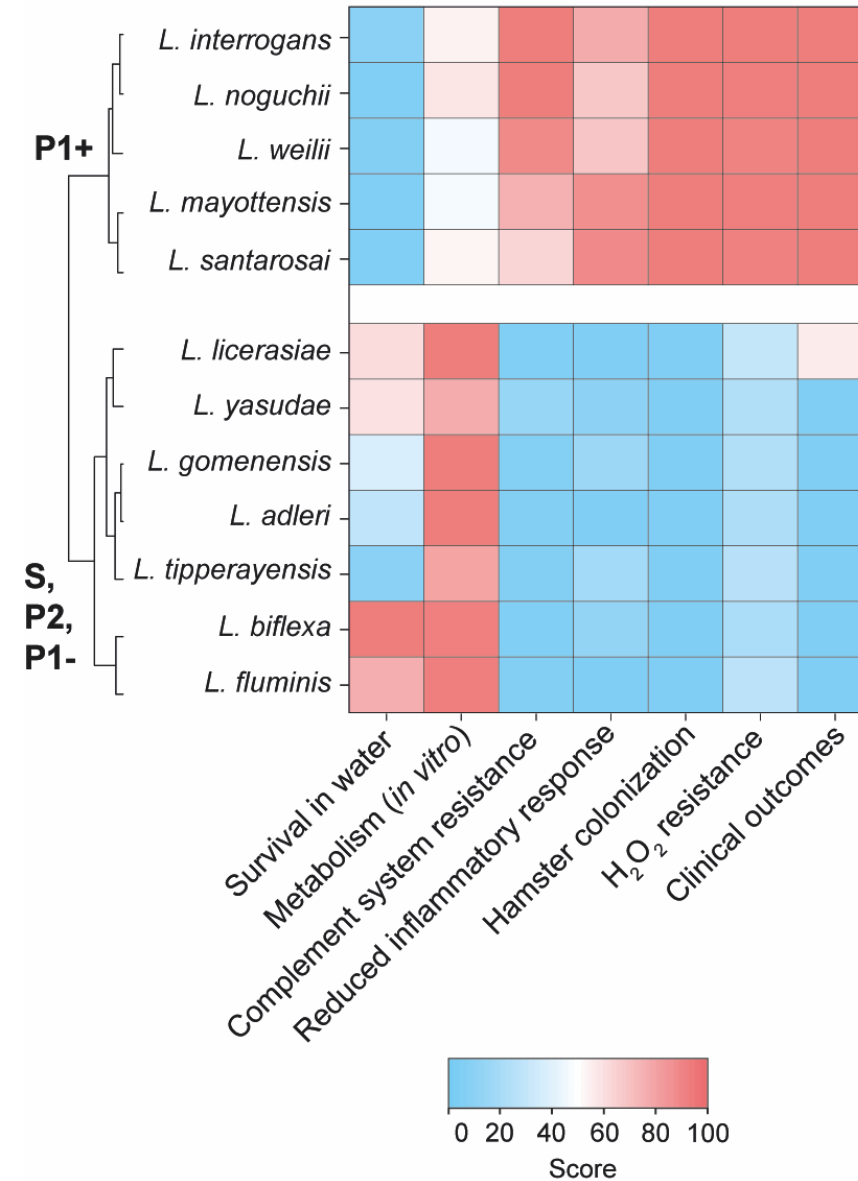
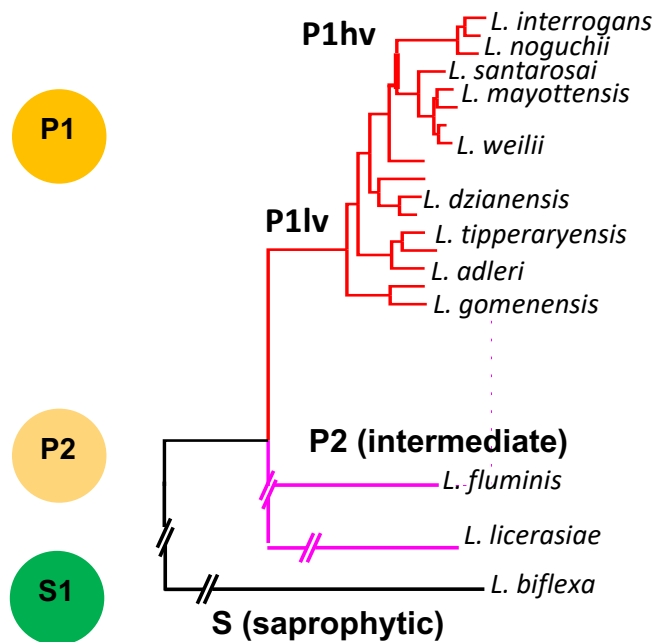


# Only P1+ species share virulence properties



Analysis of the *in vivo* and *in vitro* phenotypes

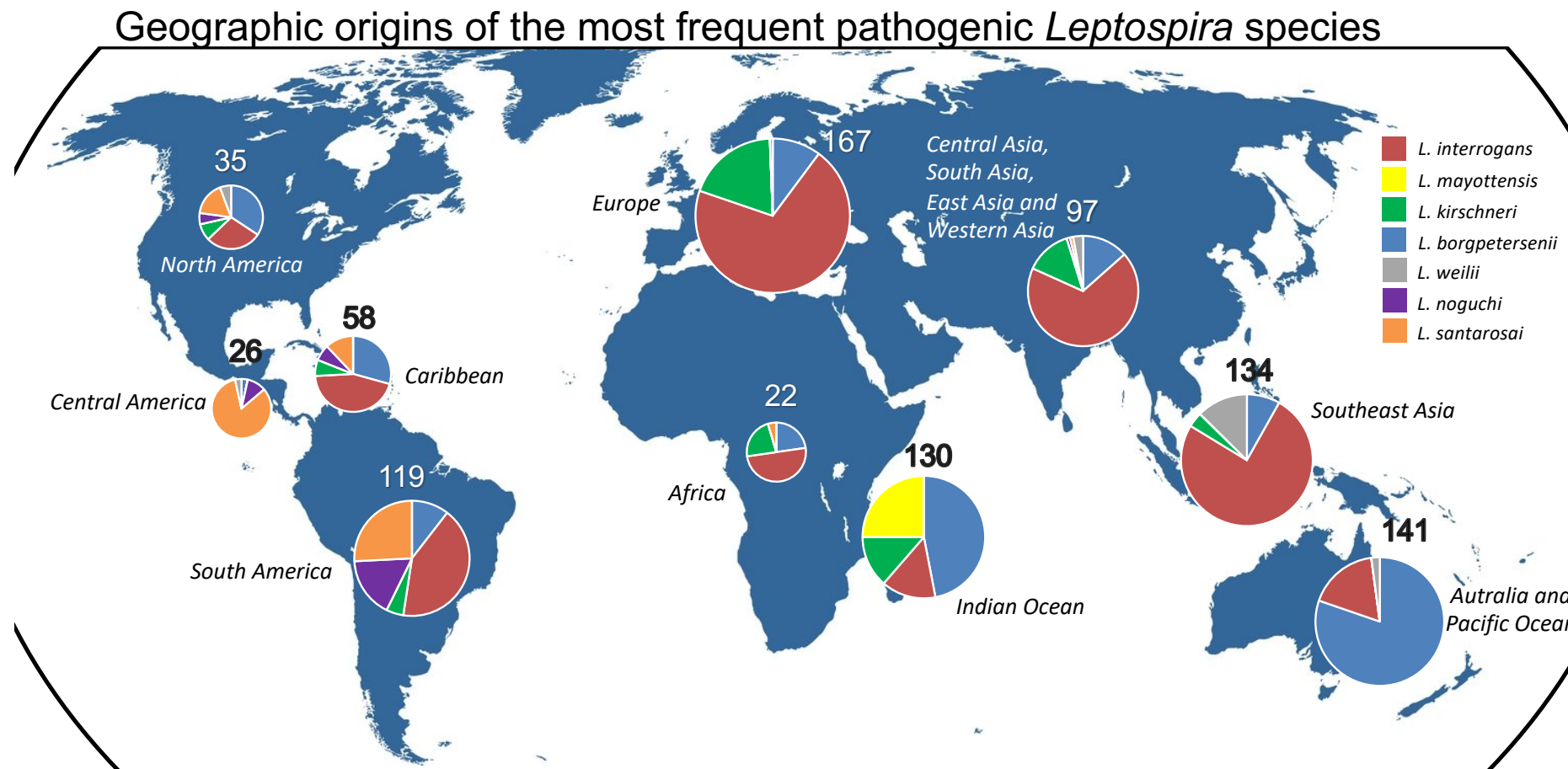
# Only P1+ species share virulence properties



Giraud-Gatineau *et al.* 2024

# Distribution of pathogenic *Leptospira* species

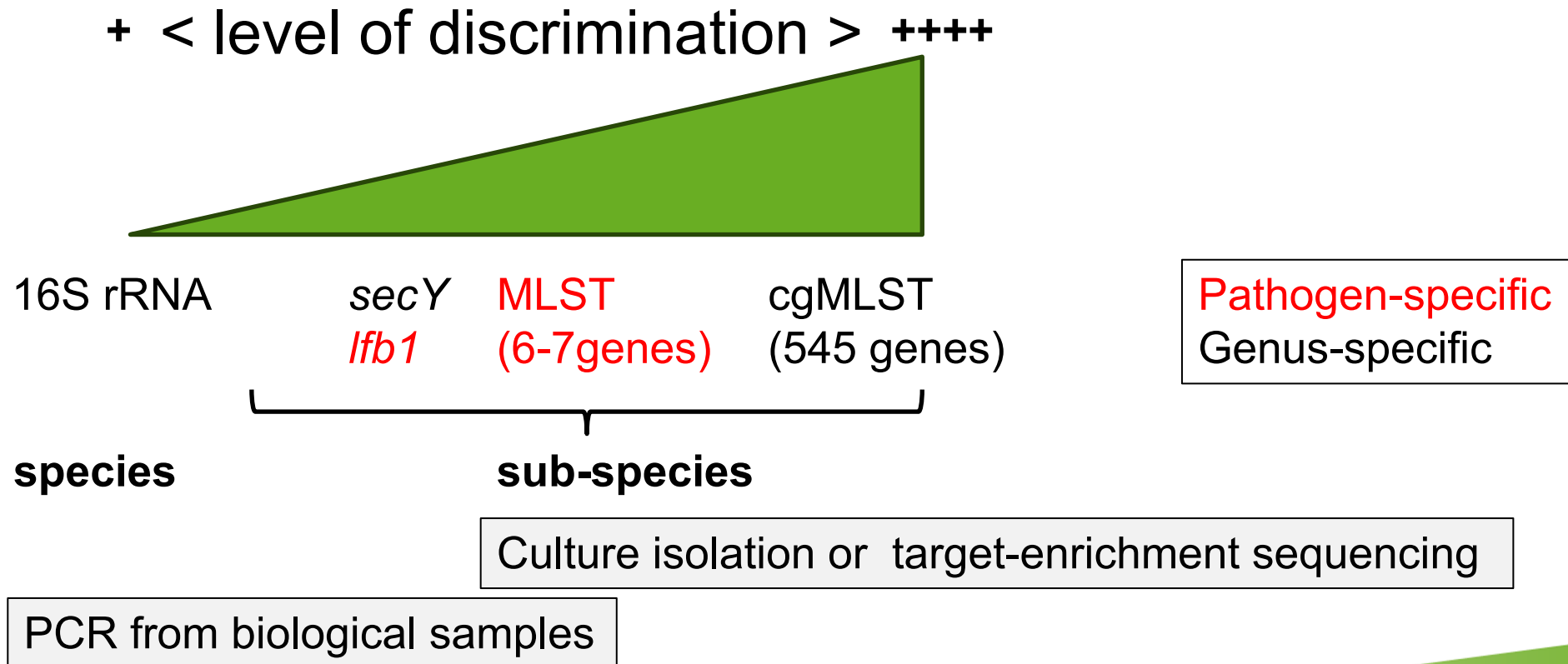
- *L. interrogans* is considered as the most common cause of leptospirosis worldwide
- Some pathogenic species are geographically restricted
- Few isolated strains in Africa



Chinchilla *et al.* 2023

# Leptospira typing

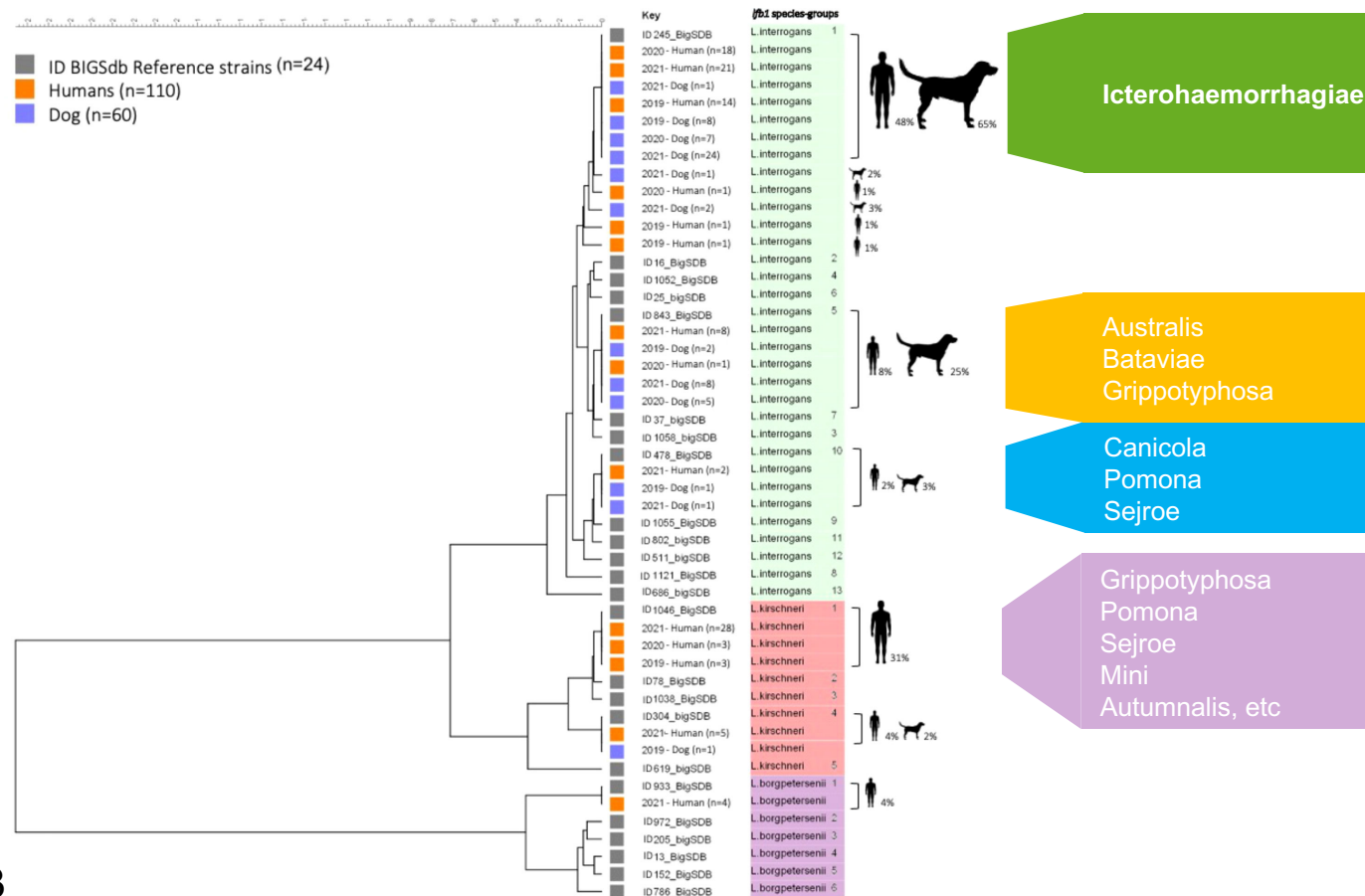
- MAT is not always a good predictor of the infecting serogroup
- Culture isolation is challenging
- Sequencing of PCR products is superior to serology (and now more accessible) for strain typing



# Direct *Leptospira* typing from biological samples

- PCR amplification and sequencing of *lfb1*, a pathogen-specific gene

Phylogenetic tree based on *lfb1* sequences from human (110) and dog (60) samples in France in 2019-2021



# Development of a universal cgMLST scheme

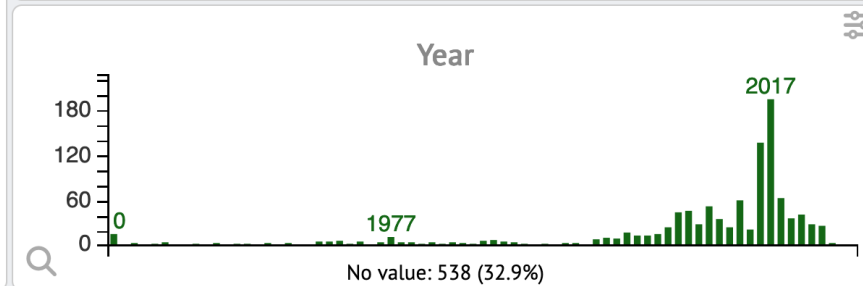
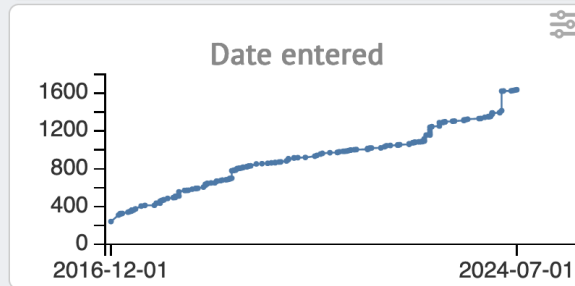
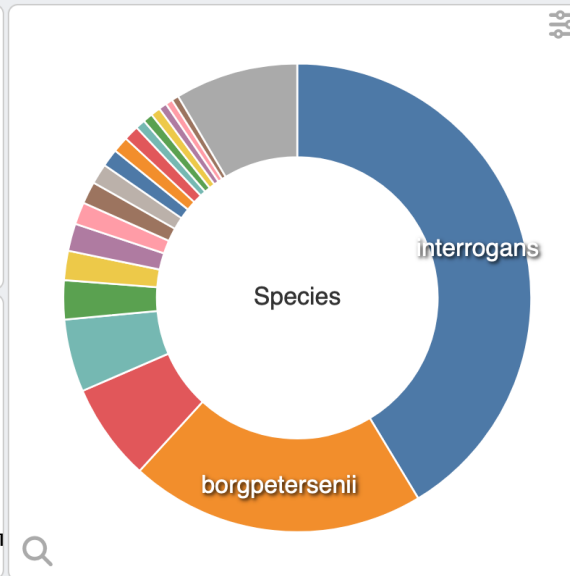
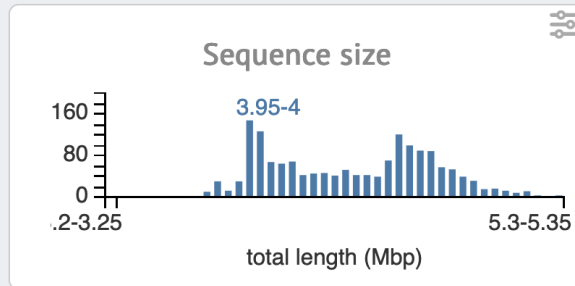
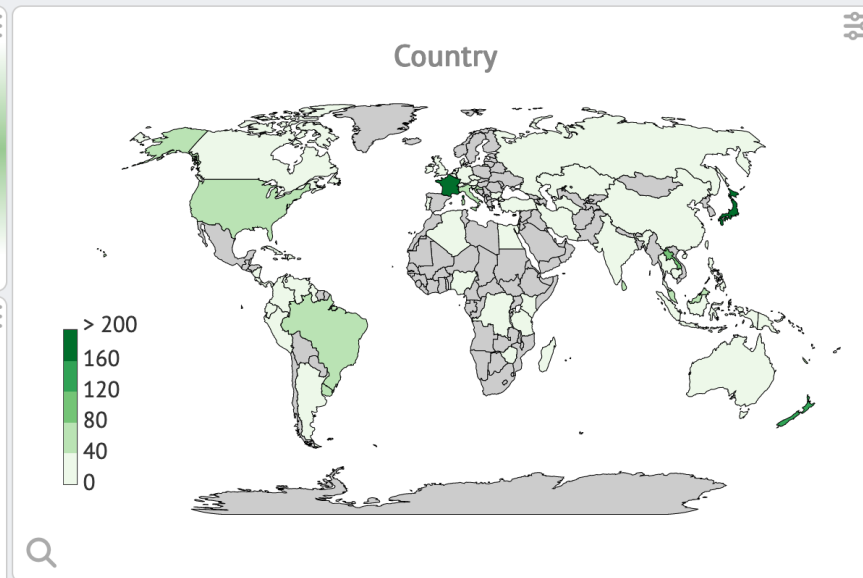
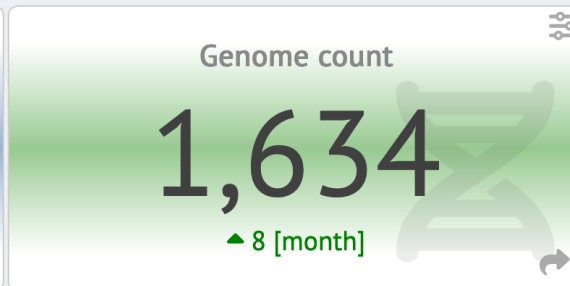
- Selection of 545 core genes from the *Leptospira* genus
- Fine-level strain discrimination for epidemiological purposes
  - cgMLST sequence type (cgST)
  - Clonal group (CG) is defined as a group of cgST differing by no more than 40 allelic mismatches out of 545 gene loci
- Online and publicly available database (>1500 genomes)
- Isolates belonging to the same CG belong to the same serogroup. Conversely, strains of a given serogroup can fall into phylogenetically unrelated CGs

# BIGSdb \_ *Leptospira* cgMLST database



## Leptospira cgMLST database

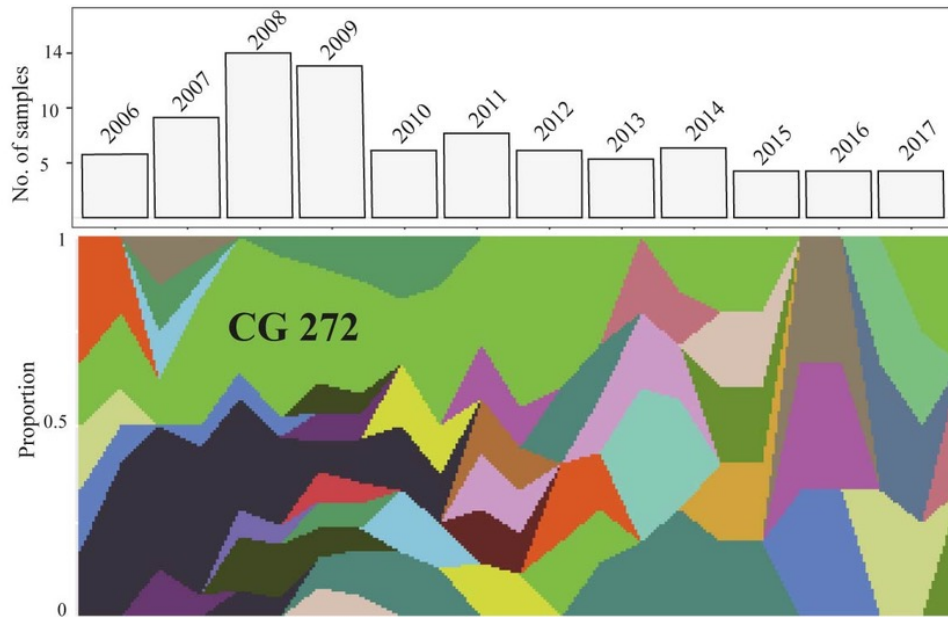
Record versions: current; Record creation: all time



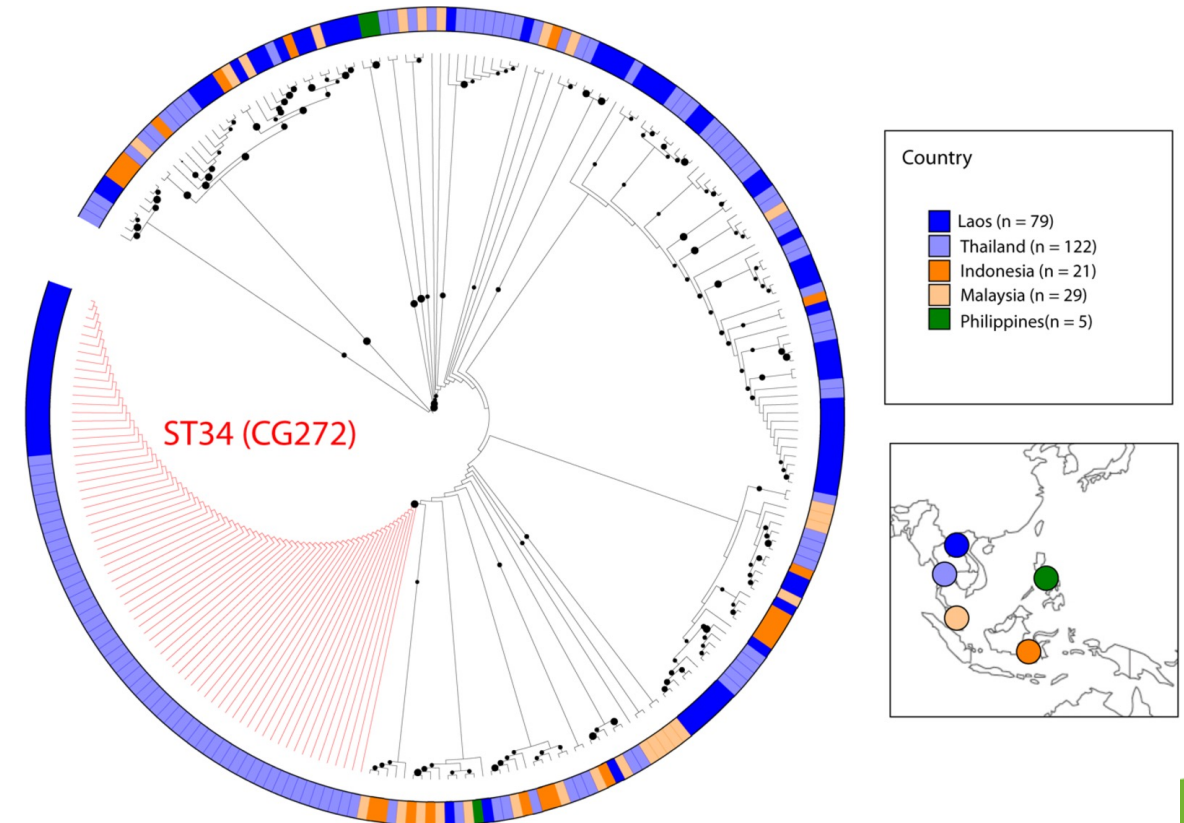
# Phylogenetic relatedness of *Leptospira* strains circulating in Southeast Asia

- Clone ST34/CG272 was recovered throughout the 12-year period in Laos and was associated with deaths, and with a large outbreak in Thailand

Distribution of clonal groups in Laos during 2006–2017



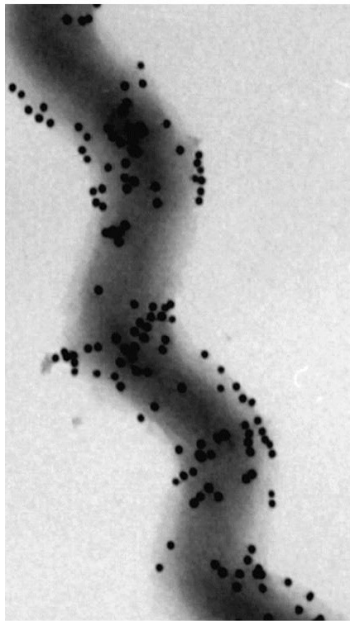
Prevalence of the ST34/CG272 strains in Laos and neighbouring countries



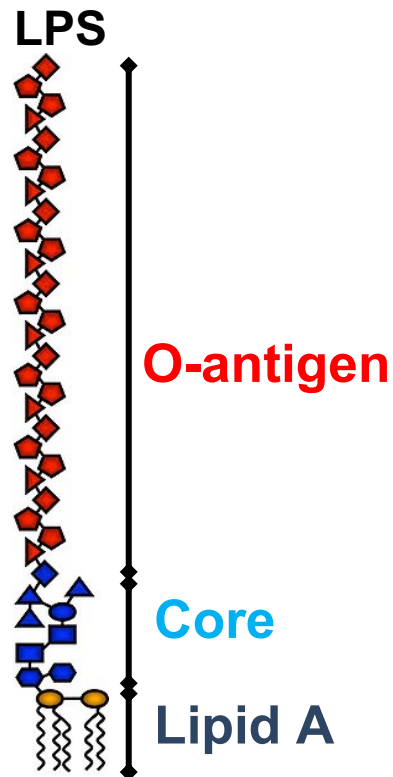
# *Leptospira* serovars / serogroups

- >300 serovars and 24 serogroups (antigenetically related serovars)
- Based on O-antigen (*rfb* locus)
- Same serovars may be found in different species
- Serovars are usually associated with animal reservoirs

*L. interrogans* coated with gold-labeled anti-LPS monoclonal antibodies



Haake *et al.* 2015



# *Leptospira* serovars found in multiple species

Serovar	Species
Bataviae	<i>L. interrogans</i> , <i>L. santarosai</i>
Bulgarica	<i>L. interrogans</i> , <i>L. kirschneri</i>
Grippotyphosa	<i>L. kirschneri</i> , <i>L. interrogans</i>
Hardjo	<i>L. borgpetersenii</i> , <i>L. interrogans</i> , <i>L. meyeri</i>
Icterohaemorrhagiae	<i>L. interrogans</i> , <i>L. inadai</i>
Kremastos	<i>L. interrogans</i> , <i>L. santarosai</i>
Mwogolo	<i>L. kirschneri</i> , <i>L. interrogans</i>
Paidjan	<i>L. kirschneri</i> , <i>L. interrogans</i>
Pomona	<i>L. interrogans</i> , <i>L. noguchii</i>
Pyrogenes	<i>L. interrogans</i> , <i>L. santarosai</i>
Szwajizak	<i>L. interrogans</i> , <i>L. santarosai</i>
Valbuzzi	<i>L. interrogans</i> , <i>L. kirschneri</i>

Levett 2001

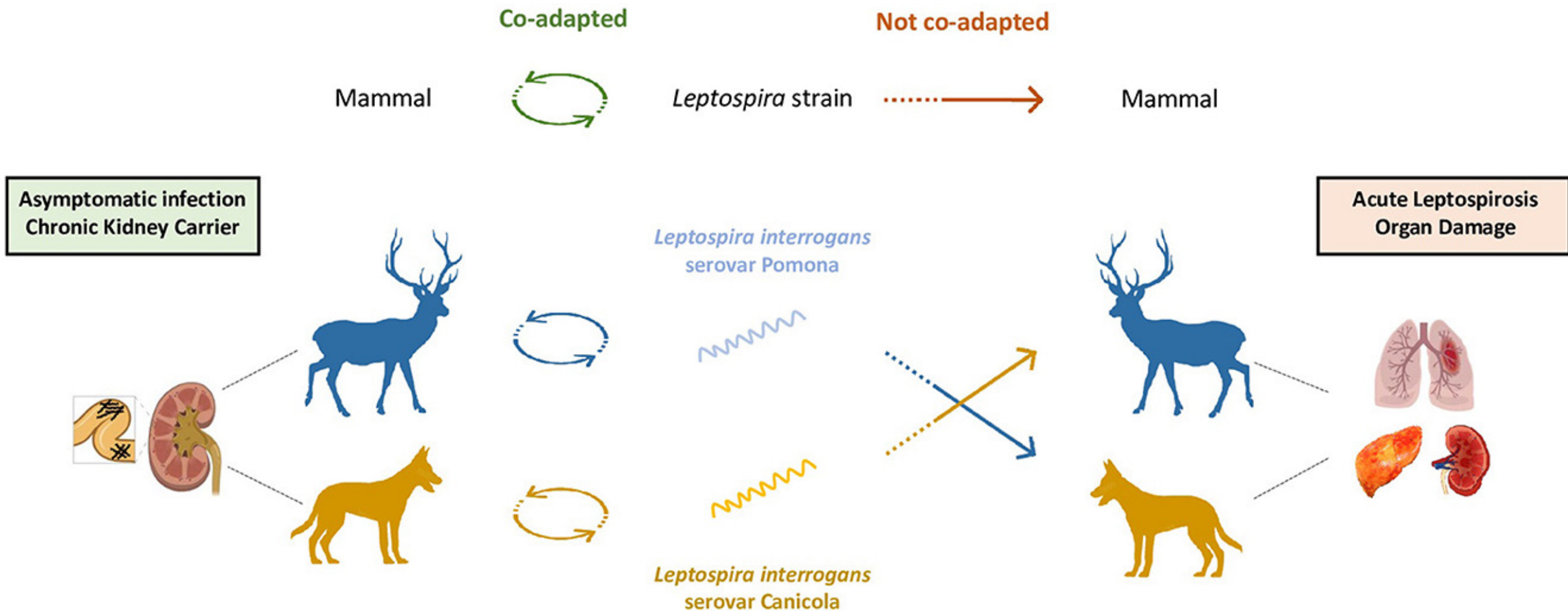
Based on data reported by Brenner *et al.* and by Feresu *et al.*

# Typical reservoir hosts of common serovars

- Animal reservoirs represent the natural source of infection and of environmental contamination

Reservoir host	Host-adapted serovars
Pig	Pomona, Tarassovi
Cattle	Hardjo, Pomona
Horse	Bratislava
Dog	Canicola
Rat	Icterohaemorrhagiae, Copenhageni
Mouse	Ballum, Arborea, Bim
Bat	Cynopteri, Wolffi

# Leptospirosis susceptibility in incidental hosts



# O-genotyping for serovar determination

- Cross-agglutinin absorption test (CAAT) is obsolete (expensive, time-consuming and performed by few reference labs)
- Complete whole genomes sequences of known serovars
- Network association analysis comparing the protein repertoire between *rfb* loci
- Protein presence/absence patterns
  - Good correspondence between gene composition of the *rfb* locus and serovar identity
  - The *rfb* locus shows signs of horizontal gene transfer





# In summary, strain typing shows that

- *Leptospira* are ubiquitous in the environment
- A great biodiversity in the genus, probably still under-estimated
  - 69 species, including 8 pathogenic species (*L. interrogans*, etc)
  - >300 serovars (Icterohaemorrhagiae, etc)
- Distribution of species and serovars varies at the region / country level
- Direct genotyping of *Leptospira* in clinical samples without culture isolation

Identification of locally circulating strains :

- Impact on PCR- and antibody-based diagnostics and vaccine efficacy

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**Patient with fever <5 days.  
Which test should be chosen for  
diagnosis?**

① Start presenting to display the poll results on this slide.

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## What is the main transmission route for leptospirosis

① Start presenting to display the poll results on this slide.

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**I want to know the serogroup of a pathogenic strain, what method should I use?**

① Start presenting to display the poll results on this slide.

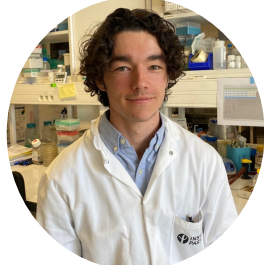
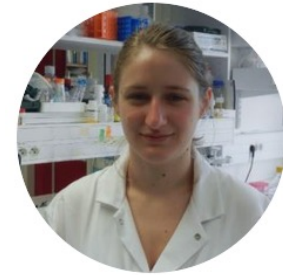
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## What are the differential diagnoses for leptospirosis ?

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**Biology of Spirochetes unit  
National Reference Center for Leptospirosis  
WHO Collaborating Center for Research and Reference on Leptospirosis**

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