Fundamental Leptospirosis Knowledge Gaps and Challenges for RD&I

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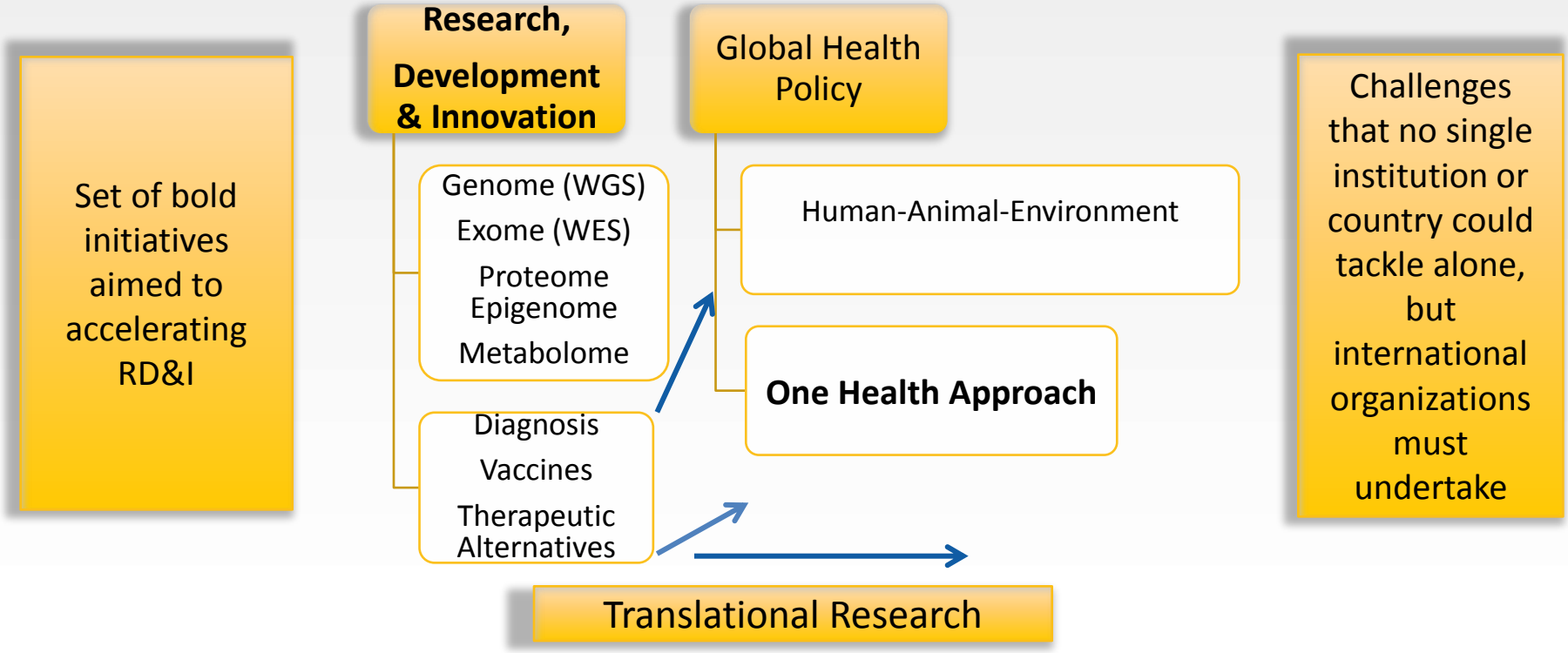
A Roadmap for Leptospirosis
Towards a Global Agenda

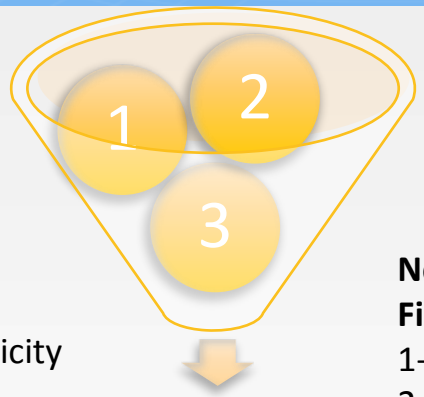


Previous Meetings, Agreed Strategic Work Plan WHO/CC IOC/FIOCRUZ and PAHO

- **Goals**
  - The Inter American Network for Leptospirosis Diagnosis and Research
  - A Research Agenda according to needs of LAC region
- **Meetings**
  - **2010** – Scientific leaders and decision maker authorities, FIOCRUZ, Rio de Janeiro. First drafts for laboratorial support , capacity building and research.
  - **2011 –** During the ILS Meeting (with permission), Merida, Mexico. Report of country needs signed by 30 participants including representatives from LAC countries and experts from other continents.

About this Session

What does fundamental knowledge gaps mean, in this context, nowadays?
At the present time, in contrast to the past …



Research Fields

1- Epidemiology
2- Bacteriology (Identification, Pathogenicity and Toxicity)
3- Immunology and Immunopatology

New Technologies and Analogous Research Fields with Possible Applications

1- Genome (WGS and WES publically available)
2- Proteome
3- Metabolome

Approaches

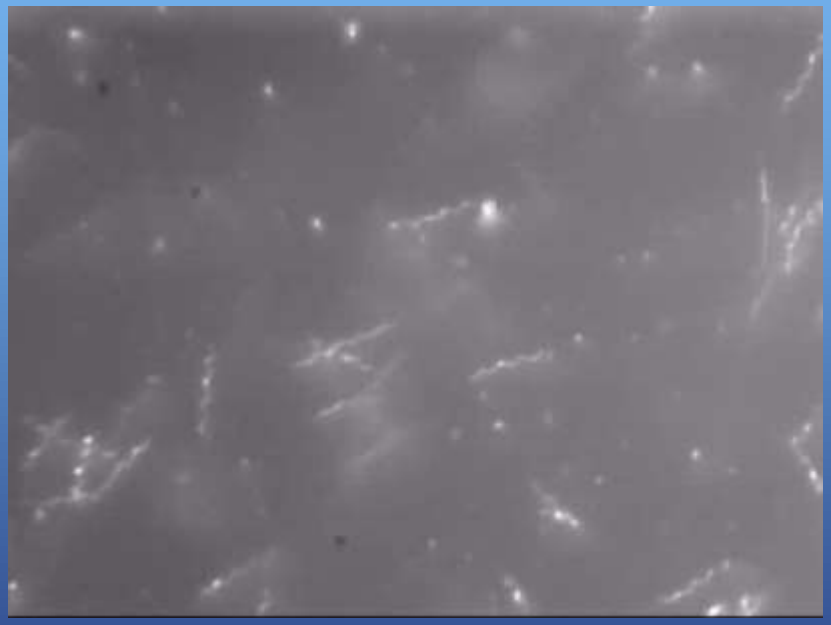
1- Identification of clinical isolates and Surveillance
2-Genome of serovar Copenhageni and applications for diagnosis and vaccines
3-Experimental Models for Understanding Pathogenesis and Host-parasite interactions

A Big Challenge for Biological Research

Biodiversity of *Leptospira*, Animal Carriers and Ecosystems

21 genome species - > 250 serovars

Leptospira



Borrelia

Movies kindly provided by Jarlath Nally and Michael Lovett, UCLA/USA

Biodiversity of Pathogenic *Leptospira* and Animal Hosts (synanthropic rodents, domestic, livestock and wild animals)

Possible Implications

1- Wide geographic distribution of the etiological agent of human or animal disease associated to the animal dispersion;
2- Challenges in creating control measures for human and animal disease;
3- Elimination of the etiological agent is likely impossible;
4- Difficulties related to laboratorial diagnosis and identification of clinical isolates;
5- Little interest in development and producing tailor-made vaccines based on conventional technologies due to the costs and benefits.

Main Conclusions:

RD&I - Only new and cutting-edge technologies will provide better solutions than the current alternatives for rapid and timely diagnosis, vaccines and clinical care.

“One Health" Operational Concept

Integrated efforts followed by policy actions should be taken at the local, national and international levels. New tools of diagnosis, vaccines for clinical care are needed.

Understanding Leptospirosis Pathogenesis

- A whole world to be explored
  - Experimental models of resistance and susceptibility
  - Cell markers
  - Toxic and hemorrhagic mechanisms
  - Possible advances for therapy and reducing morbidity and the lethality rates.

Leptospirosis Severe Forms

The severe forms of leptospirosis remains a big challenge to the clinical practice. Frequently, not supported by timely aid of laboratorial diagnosis, or scientific evidences for clinical management, physicians get involved with simultaneous needs such as:

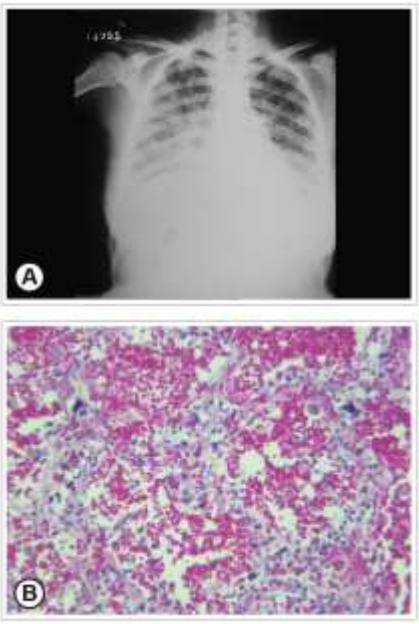
1- To combat the infection process;
2- Monitor the inflammatory process;
3- Maintain the metabolic conditions of the patient.

24,057 reported cases (2010-2015)

2,023 deaths (8,4%)

Ps. Deaths may occur in tertiary hospitals. SPFL can occur in 50% of cases who develop severe pulmonary forms. See figure showing intense hemorrhagic pneumonitis with intralveolar hemorrhage.

Figure 2



Severe Pulmonary Form of Leptospirosis

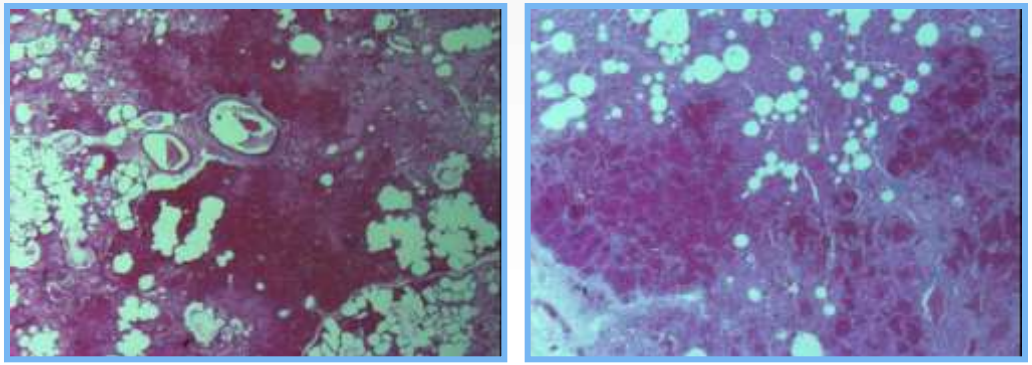
Uncommon or Rarely Recognized
Without Tools for Early Diagnosis

- The most severe clinical manifestation of leptospirosis, characterized by extensive pulmonary hemorrhage leading to respiratory failure and death by asphyxiation.
- Respiratory symptoms appear between the fourth and sixth days of illness;
- Rapid and severe course leading to death by asphyxiation in less than 72 hours after the onset of respiratory symptoms.

Hemorrhagic Lung - Human

A

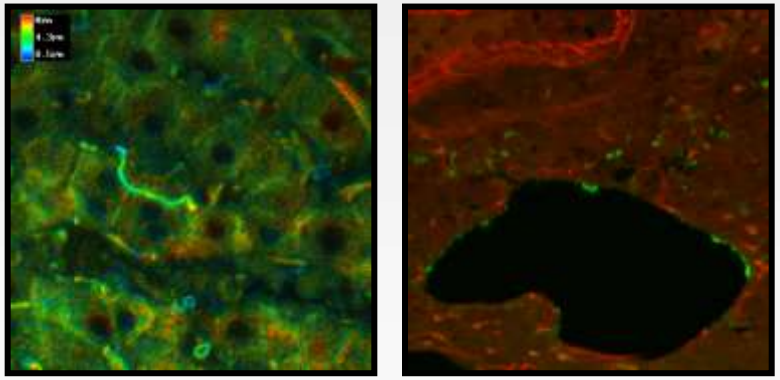
Male, 19 years old
Clinical evolution: 6 days
Lung weight: 900 g
Magnified 25 X



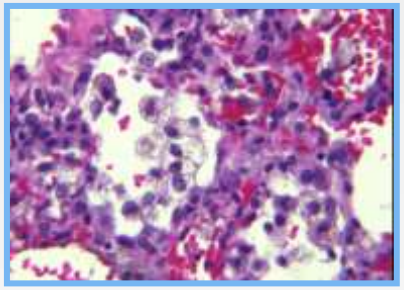
B

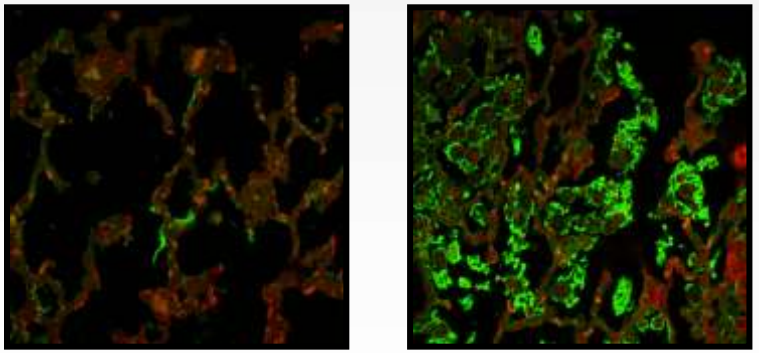
Male, 24 years old
Clinical evolution: 6 days
Lung weight: 1200 g

Antigens and Immunohistological Findings
Experimental model of susceptibility (marmosets mimics human disease)



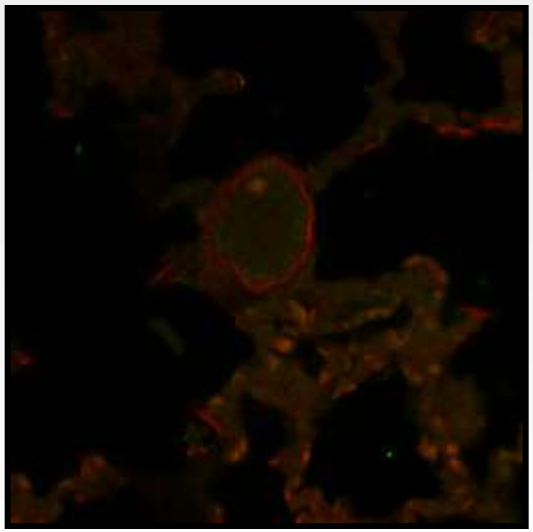
Antigens in liver and lung of infected marmoset monkey
Confocal laser scanning microscopy



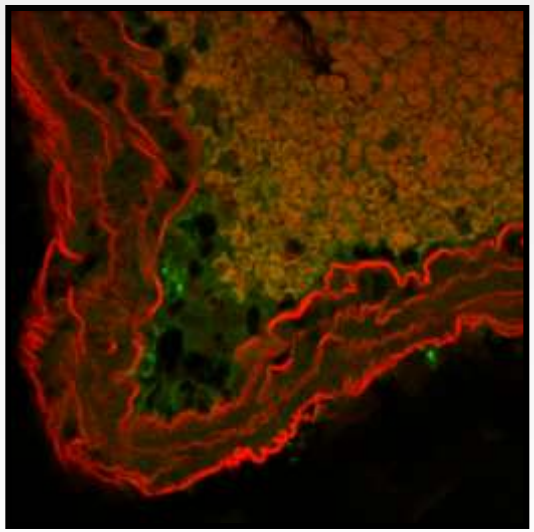


IgA in hemorrhagic lung of infected marmoset monkey. 6 p.i.d and 9 p.i.d.

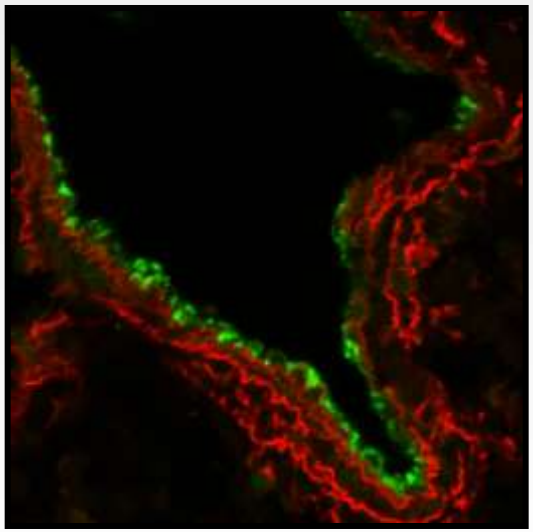
Immunohistological Findings – Marmoset Monkeys
Factor VIII – *Down Regulation*
Possible connection with causes of hemorrhage



6 p.i.d



18 p.i.d



24 p.i.d

Nota: *Down regulation* of clotting factors in the acute phase.

Mui

Translational Research Definitions

- **Definitions**
- *Translational research fosters the multidirectional integration of basic research, patient-oriented research, and population-based research, with the long-term aim of improving the health of the public. T1 research expedites the movement between basic research and patient-oriented research that leads to new or improved scientific understanding or standards of care. T2 research facilitates the movement between patient-oriented research and population-based research that leads to better patient outcomes, the implementation of best practices, and improved health status in communities. T3 research promotes interaction between laboratory-based research and population-based research to stimulate a robust scientific understanding of human health and disease.*

Síndrome Pulmonar Hemorrágica em Humanos e Infecção Experimental em Primatas não Humanos

Conclusões

- Cepas recém isoladas de casos humanos com SPHL causam hemorragia pulmonar intensa e grave em primatas não humanos da espécie *Callithrix jacchus;*
- Os achados histopatológicos mimetizam a doença humana e são comparáveis nos dias 9-12 após inoculação;
- Os infiltrados intersticiais apresentam números variáveis de monócitos/macrófagos, linfócitos, neutrófilos, megacariócitos e mastócitos em degranulação.
- A diátese hemorrágica é aguda, não necessáriamente associada com extravasamento de plasma e proteínas. É agravada por trombocitopena, seguida de reação de megacariócitos e degranulação de mastócitos;
- A hemorragia intra-alveolar não é um aspecto comum em outras síndromes que cursam com insuficiência respiratória auda como dengue hemorrágico e síndrome pulmonar por Hantavirus.