## Steering Committee 23-24 January 2018 – Phnom Penh

# Human leptospirosis in urban and peri-urban areas of Yangon region, Myanmar

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ECOMORE II

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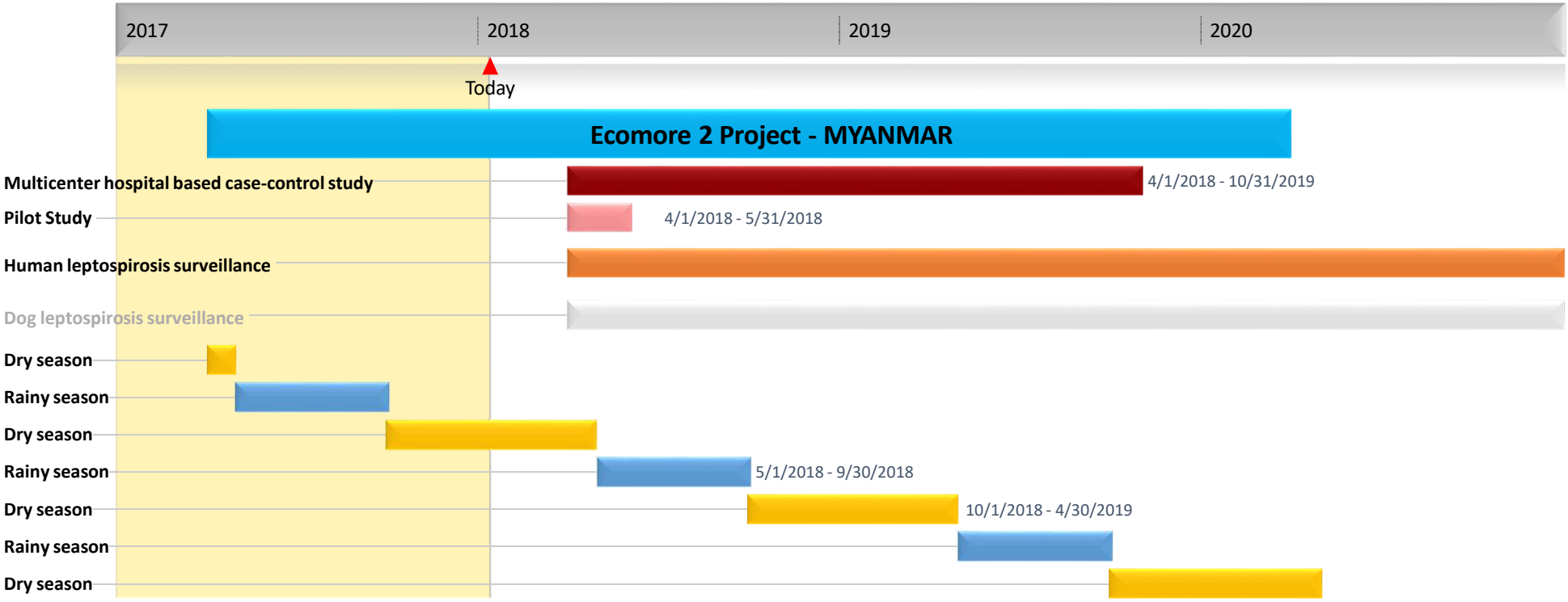



- PRIMARY OBJECTIVE OF THE PROJECT -

*To set up the response capacity of Health authorities and Health community to reduce morbidity and mortality due to leptospirosis and to improve health of populations most affected by flood and heavy rainfall in urban and peri-urban environment*

# Process of initiation of the project

- **Relevance at the national level**
  - Myanmar is prone to extreme weather events, especially very heavy rains floods and cyclones, all of which are predicted to increase because of climate change
  - Flooding has always been one of the major natural hazards in Myanmar
  - In Myanmar, leptospirosis remains under-diagnosed. Laboratory diagnostic capacity should be strengthened especially in central, district and township-level hospitals. Animal sector should also be strengthened for surveillance of leptospirosis.

*Project in accordance with the National Health Plan (2017-2021 ) Strategy from the Ministry of Health and Sports*

- **Involvement of Authorities**
- **MOHS (MS, Clinicians)**
  - *To start the Knowledge Translation from the beginning of the project.*
  - *To provide awareness of the Authorities before starting of the project by advocacy meeting.*
  - *To discuss with the partners about the content of the project*

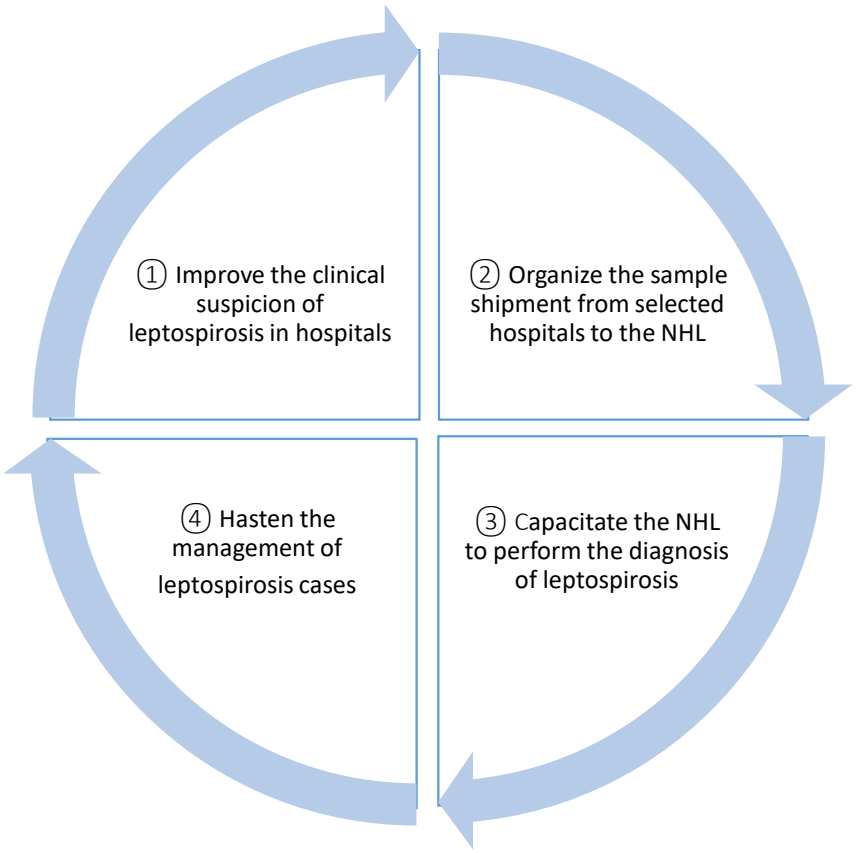
**(After Project Agreement)**

- The study has been shaped by **transversal collaboration** between NHL, IP New Caledonia (Dr. C. Goarant) and IP Cambodia (Dr. P. Piola).

# Laboratory and hospital capacity building can improve post-disaster management of emerging diseases

*Yankin Children Hospital*

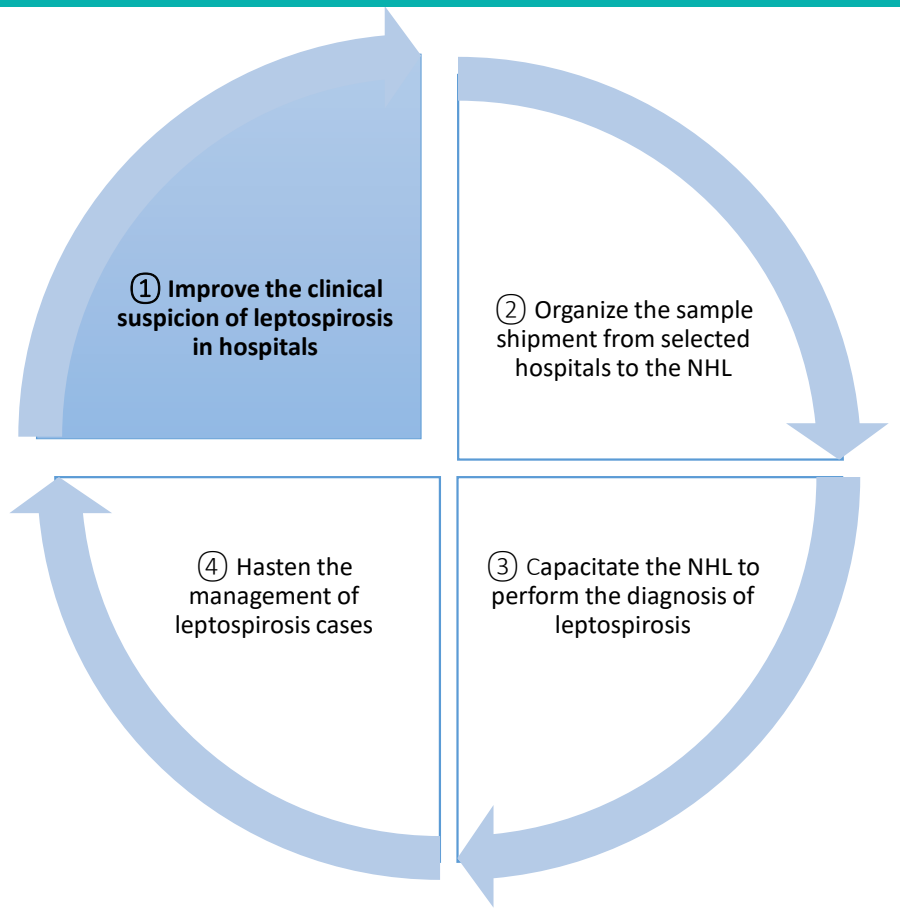
*Yangon General Hospital*




*National Health Laboratory (NHL)*

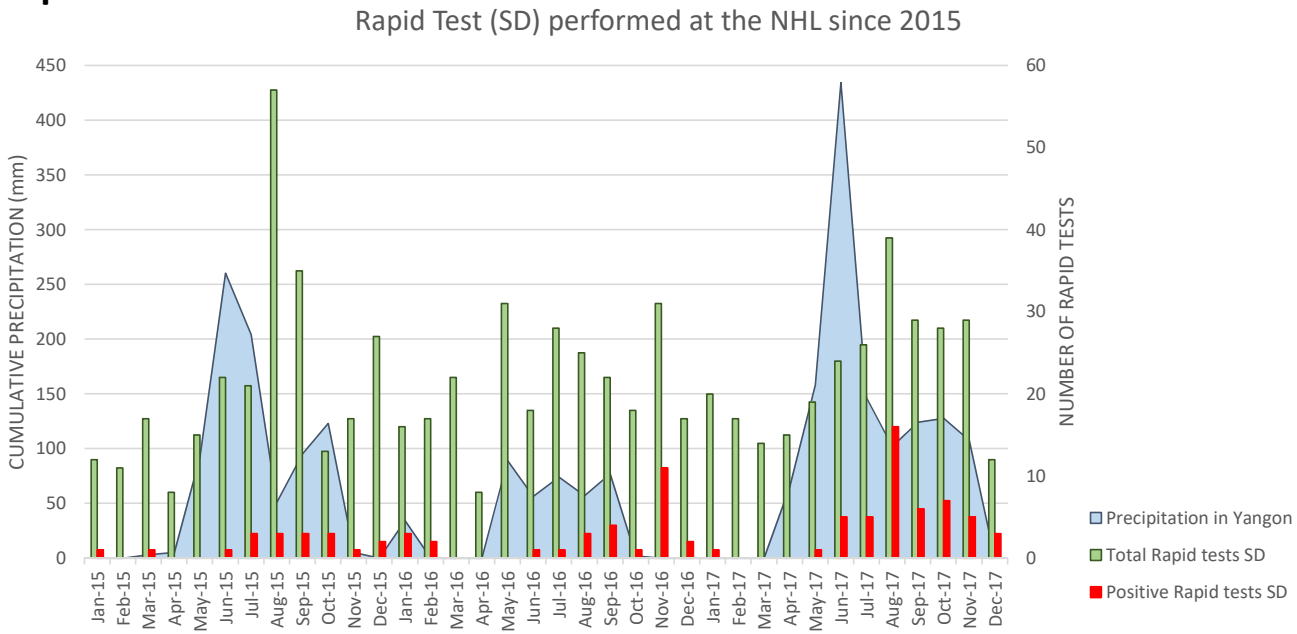
# ① Improve the clinical suspicion of leptospirosis in hospitals

*Outpatient department in Yangon*



# ① Improve the clinical suspicion of leptospirosis in hospitals

At the NHL so far, **only serological diagnosis** for leptospirosis available;
The Medical Doctors request the type of test they need, Rapid tests are performed immediately, ELISA once a week;
**Only one-time serology**, no paired sera analysis;
For positive samples, **a few data** can be retrieved at NHL (date of analysis, initials, age, gender and result) but **not all samples**



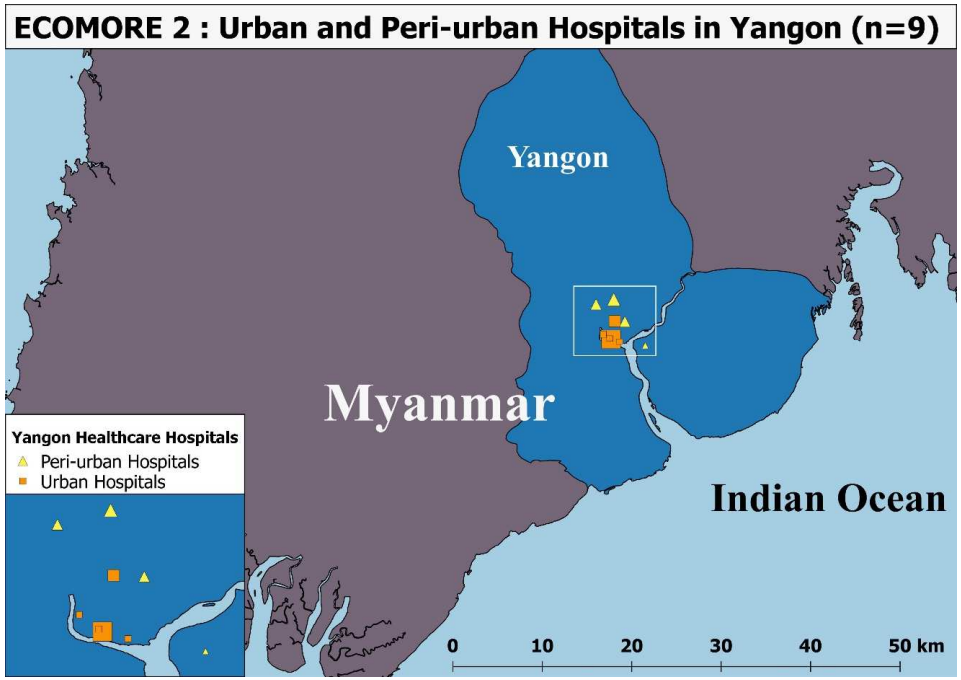

**Rapid tests (SD) >> ELISA Panbio**

| Year | Total Rapid Test | Positive | Total ELISA Panbio | Positive |
|---|---|---|---|---|
| 2011 | 255 | 57 (22%) | - | - |
| 2012 | 170 | 13 (7.5%) | - | - |
| 2013 | 197 | 13 (6.5%) | - | - |
| 2014 | 233 | 10 (4.3%) | - | - |
| 2015 | 255 | 18 (7%) | - | - |
| 2016 | 253 | 28 (11%) | 6 | 5 ( 83%) |
| 2017 | 272 | 49 (18%) | 3 | 1 (33%) |

# ① Improve the clinical suspicion of leptospirosis in hospitals

## Selection of 9 public hospitals covering both urban and peri-urban areas of Yangon region

| Name | # of beds | Area |
|---|---|---|
| Yangon General Hospital | 2000 | Urban |
| New Yangon General Hospital | 200 | Urban |
| East Yangon General Hospital | 200 | Urban |
| Western Yangon General Hospital | 200 | Urban |
| Yankin Children Hospital | 550 | Urban |
| North Okkalapa Teaching and General Hospital | 800 | Peri-urban |
| Thingangyun Sanpya General Hospital | 500 | Peri-urban |
| Insein General Hospital | 500 | Peri-urban |
| Thanlyin Hospital | 200 | Peri-urban |




Done  Ongoing

# ① Improve the clinical suspicion of leptospirosis in hospitals

To develop an <u>algorithm for case management</u> of suspected cases of leptospirosis

- Inspired from the WHO Faine's criteria (part A. Clinical signs)
- Adapted during **awareness trainings for Medical Doctors and nurses** at the selected hospitals during the pilot period [April 18-May 18]
- Agreement of principle for **expert consultancy** by Dr. Colleen Lau with local clinicians [March-April 18]

Done  Ongoing

Australian National University

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Flag this profile

## ① Improve the clinical suspicion of leptospirosis in hospitals

- Write **SOPs**[1] to assign responsibilities and roles for screening, interviewing and sampling patients [November 17- December 17]

  **Plan to** - Visit and consulting with hospital staff [February 18- March 18]
  - Feedback from hospital staff during the pilot period [April 18- May 18]

  (**After approval of Technical Agreement**)

- Design and provide necessary **data collection documents** (case report forms) and **posters on suspicion and analysis algorithms** for patients and hospital staff

- Providing **equipment to properly screen** patients (tympanic thermometer, urine strips) at the outpatient departments

[1] Standard Operational Procedures

## ① Improve the clinical suspicion of leptospirosis in hospitals

- Recruitment of **3 local project coordinators** for 20 months

  **Medical Doctors and project focal points** hosted by the NHL

  in charge of:

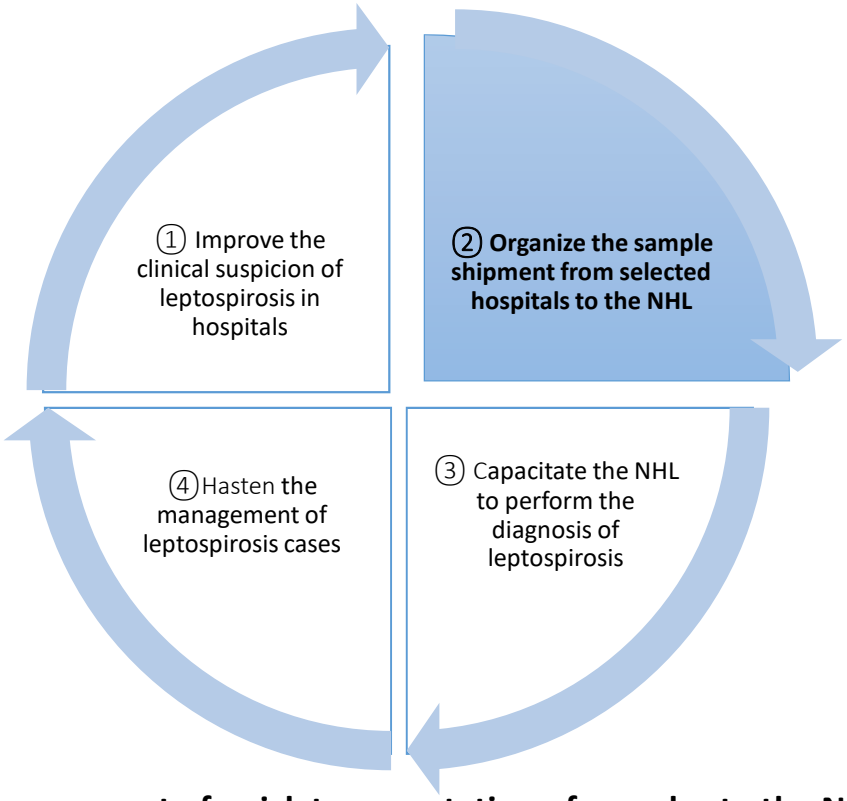
  **checking collected data**,

  **providing operational and technical support** to hospital staff,

  **communicating results** to Medical Doctors and

  **achieving the sampling scheme** i.e. 2 sera per suspected case, the second sera collected at the patient's household

# ② Organize the sample shipment from selected hospitals to the NHL



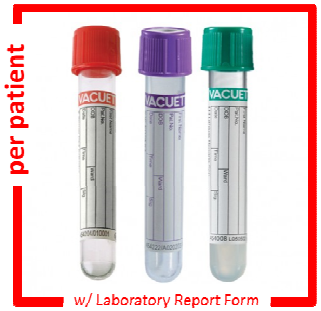

**→ Management of quick transportation of samples to the NHL**

*Traffic in Yangon*

## ② Organize the sample shipment from selected hospitals to the NHL

- Write a **SOPs** to assign responsibilities and roles for properly collecting, transporting and delivering samples [November 17- December 17]

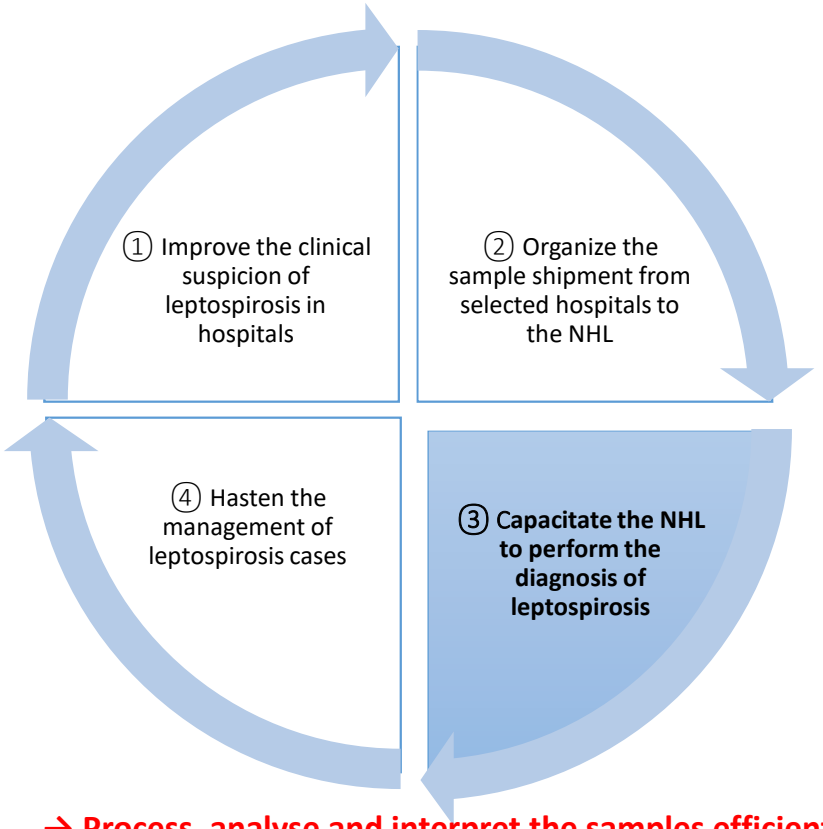
- Recruitment of a **project driver** for 20 months
- Purchase of **one car** and **equipment** for sample transportation




Expected result: shorten the delay between sample collection and result communication **≤ 2 days for qPCR**

Mean of verification: control of date mentioned on forms during the study period

# ③ Capacitate the NHL to perform the diagnosis of leptospirosis




**→ Process, analyse and interpret the samples efficiently at the bacteriology unit**

*Bacteriology Unit, NHL*

# ③ Capacitate the NHL to perform the diagnosis of leptospirosis

*Flood in Yangon*

Implementation of techniques for diagnosis of the major waterborne diseases:

- **Implement trainings needed**
- **Provide necessary reagents and equipment**

For leptospirosis diagnosis in particular (blood samples only)

- Promote the usage of ELISA Panbio® *versus* Rapid test
- Set up qPCR technique to detect bacteremia in the early stage of the disease
- Set up culture of leptospires for genotyping

For hepatitis A, E and schistosomiasis diagnosis (on the same blood samples), provide ELISA test according to the budget and expected support of TICA

## ③ Capacitate the NHL to perform the diagnosis of leptospirosis

### Trainings

- Regional course Oceania at IPNC "Leptospires and Leptospirosis" [13-17 November 17]

  **Academics sessions** to increase the knowledge on leptospirosis, especially biology of leptospires and epidemiology of the disease to reinforce surveillance, diagnosis and control of the disease in the region

  **Laboratory sessions** on ELISA, MAT, PCR and culture

- Training qPCR at the NHL **[first training on the 25-26 January 18]**

- Training culture at the NIHE [Before April 18]

## ③ Capacitate the NHL to perform the diagnosis of leptospirosis

Provision of the necessary **resources**, **equipment and reagents** at the NHL

- Characterization of the **protocol for qPCR** [before March 18]

  Primers LipL32 for the detection of pathogenic *Leptospira* only, not nonpathogenic nor intermediately pathogenic *Leptospira* spp.

  Should we investigate PCR inhibition with RNAse P ? systematically or only on PCR negative samples ?

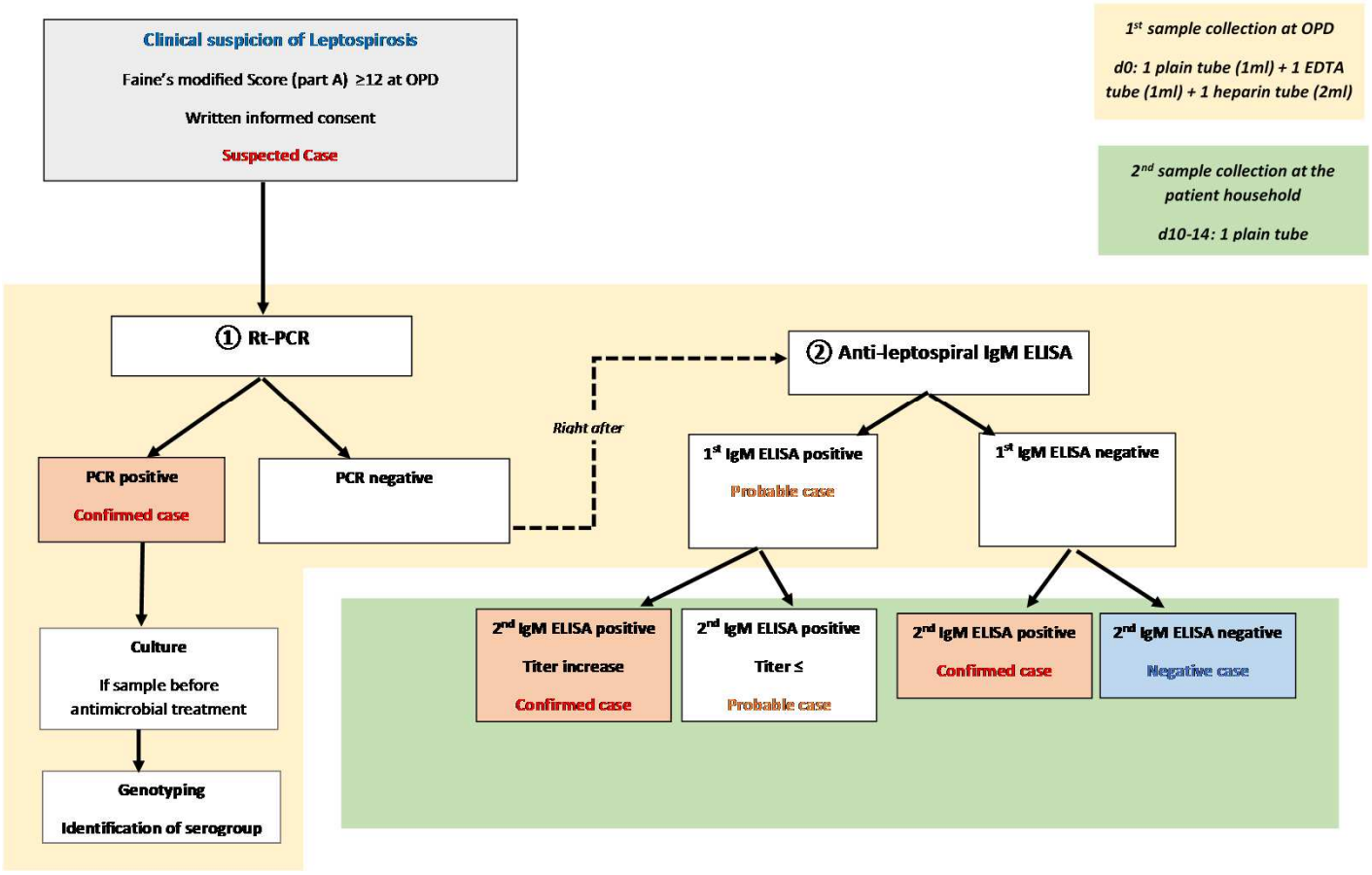
  Should we test PCR negative samples with degenerate primers? To extend the serovar detection, huge benefit for serovars alexanderi and mayottensis, minor benefit for serovar weilii

- Gathering of quotations of identified local suppliers [before February 18]

- Recruitment of **2 lab technicians** for 22 months, dedicated for the project analysis [February 18- March 18]

- **External support** by IPNC: establish of support contract for one year [April 2018- March 2019]

# ③ Focus on the algorithm for analysis and interpretation




## For leptospirosis

A combination of **qPCR ± ELISA IgM** on acute-phase sample
Second **ELISA IgM** on convalescent-phase sample if needed

Clear patient status for clinicians: confirmed / probable / negative

For qPCR positive patient, **culture** for identification of circulating pathogenic strains

**Algorithm to be assessed during the pilot study**

# ③ Capacitate the NHL to perform the diagnosis of leptospirosis

Expected results:

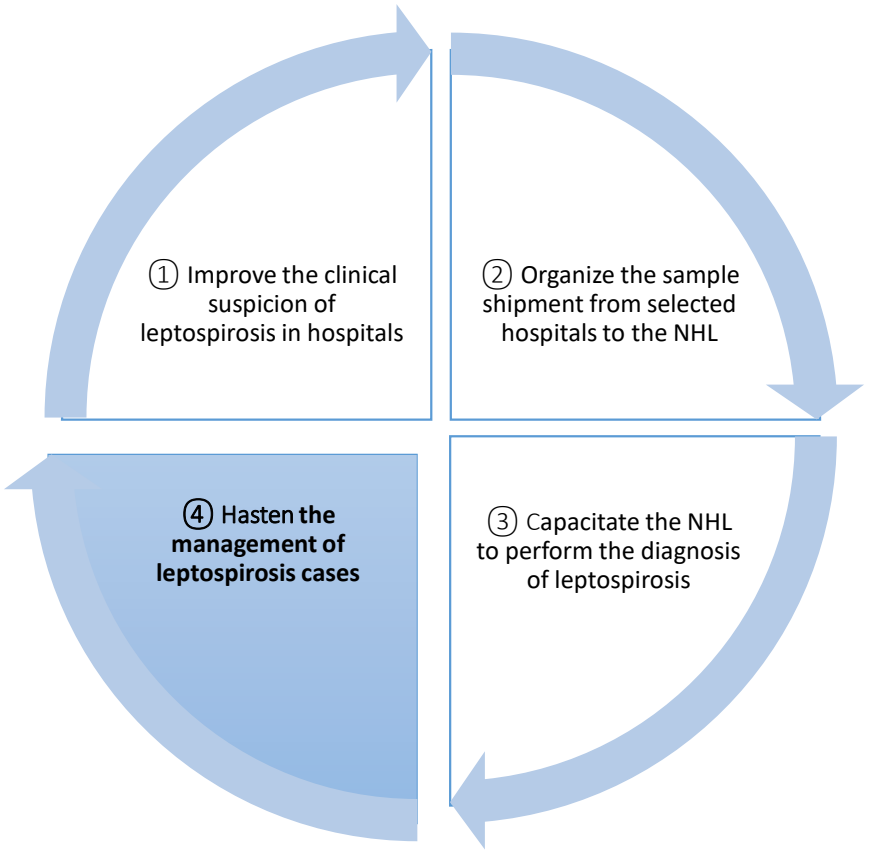
Starting from April 2018, NHL would be capable to:

- **perform analysis**,
- **interpret complex results** for Medical Doctors to improve case management,
- **perform properly leptospires culture** to provide sample for external genotyping,
- outside any major climatic event, **quantify cases during heavy rains *versus* dry season** (Annual Technical report) and help determining an epidemic threshold.

Mean of verification: Number of analysis performed, interpretation sent to Medical Doctors (logbooks), listing of pathogenic strains, external support by IPNC

# ④ Hasten the management of leptospirosis cases


*Yangon General Hospital*




**→ Provide a prompt feedback to the Medical Doctors**

## ④ Hasten the management of leptospirosis cases

- Write a **SOPs** to assign responsibilities and roles for communicating lab results and providing support to participating Medical Doctors [November 17- December 17]

- The **3 local project coordinators** mentioned before will ensure **a prompt result communication** for all suspected patients to the participating Medical Doctors

Expected result:

Shorten the delay between sample collection and result communication **≤ 2 days for qPCR** and **improve the case management downstream**

# Laboratory and hospital capacity building can improve post-disaster management of emerging diseases

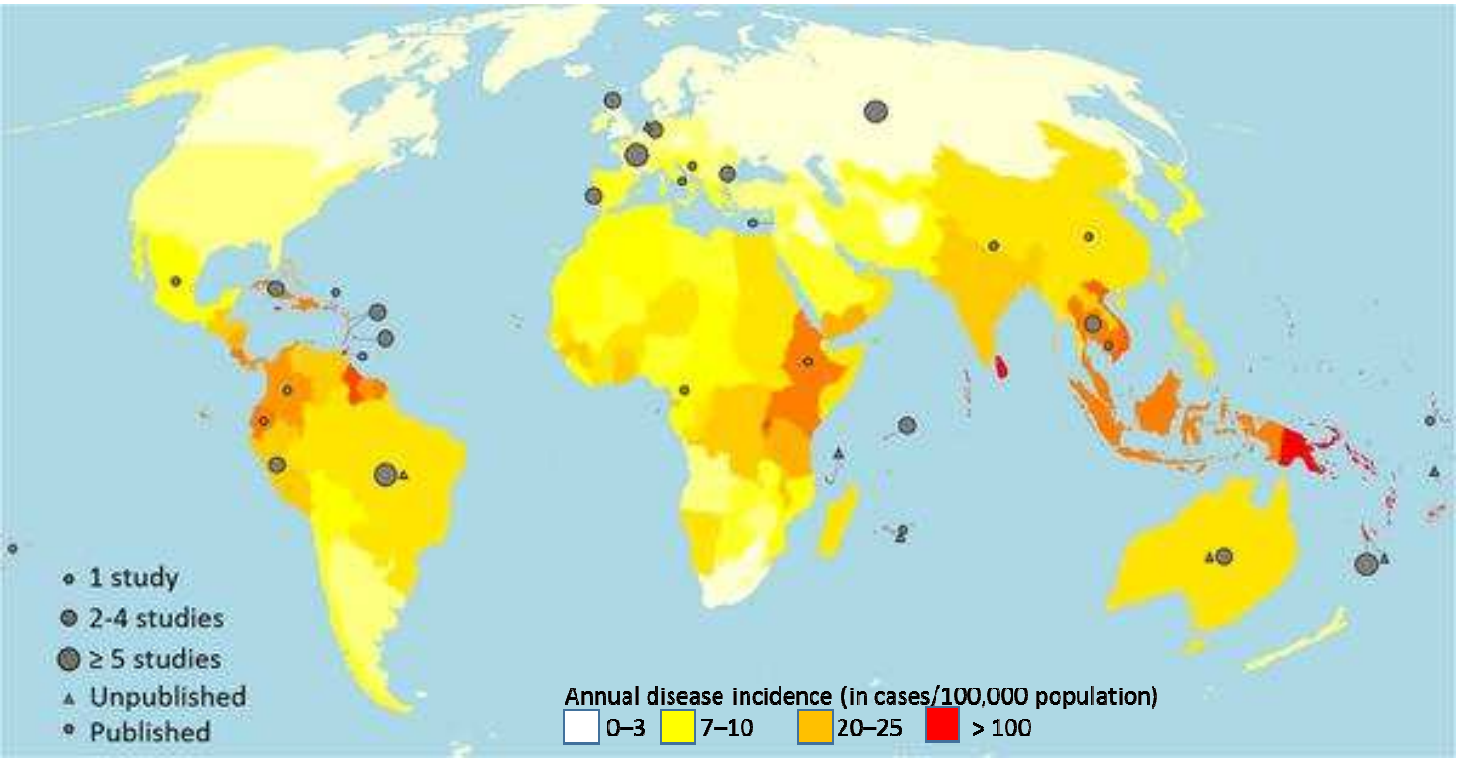

① Improve the clinical suspicion of leptospirosis in hospitals

② Organize the sample shipment from selected hospitals to the NHL

③ Capacitate the NHL to perform the diagnosis of major waterborne diseases

④ Hasten the management of leptospirosis cases

# Leptospirosis in Myanmar is suspected to be endemic but remains underdiagnosed




**Estimated annual morbidity of leptospirosis by country or territory (Costa et al, 2015)**

< 250 samples of suspected cases per year at the NHL compared to ~ 5000 cases reported each year to the Epidemiology Unit in Sri Lanka

A capacitation of NHL and selected hospitals aims at improving detection and surveillance of suspected leptospirosis.

A case-control study will set the foundations of improved leptospirosis detection and surveillance in Myanmar.

# Hospital based case-control study / OBJECTIVES and DESIGN

**Objectives:**

- Identify the determinants for human leptospirosis cases in urban and peri-urban areas in Yangon region
- To assist the design of a relevant and sustainable surveillance of leptospirosis for Myanmar

**Case-control study design**= comparison of past exposures between leptospirosis cases and non leptospirosis patients (in OPDs from 9 hospitals in Yangon region) to identify determinants.

In this study:

Case = laboratory-CONFIRMED clinically suspected case of leptospirosis

Control = laboratory-NEGATIVE clinically suspected case of leptospirosis

***First study on leptospirosis to date in Myanmar***

# FAINE'S Score (WHO 2012)

## **Suspected case** (in this study)

Inclusion criteria:

- Aged ≥ 5 years old,
- Living in Yangon region for ≥ 1 month before recruitment,
- Presenting a Faine's score part A ≥ 12 at the screening interview,
- Written consent from the patient or the accompanying person

Exclusion criteria: critically ill patient with accompanying person unable to answer for ICF

**WHO Guidelines: Modified Faine's Criteria with amendment (2012)**

| | | | |
|---|---|---|---|
| **A. Clinical data** | | | |
| Has the patient: | | | |
| Headache of sudden onset? | Yes [_]1 | 2 | |
| | No [_]0 | 0 | |
| Fever? | Yes [_]1 | 2 | |
| | No [_]0 | 0 | |
| If "yes" is the temperature 39°C or more? | Yes [_]1 | 2 | |
| | No [_]0 | 0 | |
| Conjunctival suffusion (bilateral)? * | Yes [_]1 | 4 | |
| | No [_]0 | 0 | |
| Meningism? * | Yes [_]1 | 4 | |
| | No [_]0 | 0 | |
| Muscle pain (especially calf muscle)? * | Yes [_]1 | 4 | |
| | No [_]0 | 0 | |
| Are all 3 features * present together? | Yes [_]1 | 10 | |
| | No [_]0 | 0 | |
| Jaundice? | Yes [_]1 | 1 | |
| | No [_]0 | 0 | |
| Albuminaria or nitrogen retention? | Yes [_]1 | 2 | |
| | No [_]0 | 0 | |
| Haemoptysis/Dyspnoea | Yes [_]1 | 2 | |
| | No [_]0 | 0 | |
| | | Score part A:_____ | |
| **B. Epidemiological factors** | | | |
| Rainfall | Yes [_]1 | 5 | |
| | No [_]0 | 0 | |
| Contact with contaminated environment | Yes [_]1 | 4 | |
| | No [_]0 | 0 | |
| Animal contact | Yes [_]1 | 1 | |
| | No [_]0 | 0 | |
| | | Score part B:_____ | |
| **C. Bacteriological findings** | | | |
| Isolation of leptospires in culture | | | **Diagnosis certain** |
| Positive serology | | | |
| ELISA IgM positive*; SAT positive*; MAT single high titer* | Yes [_]1 | 15 | |
| (Any one of the three tests only should be scored) | No [_]0 | 0 | |
| MAT rising titer (paired sera) | Yes [_]1 | 25 | |
| | No [_]0 | 0 | |
| | | Total:_____ | |

A presumptive diagnosis of leptospirosis may be made if:

Part A and B score 26 or more (Part C laboratory report is usually not available before fifth day of illness; thus it is mainly a clinical and epidemiologic diagnosis during early part of disease) or

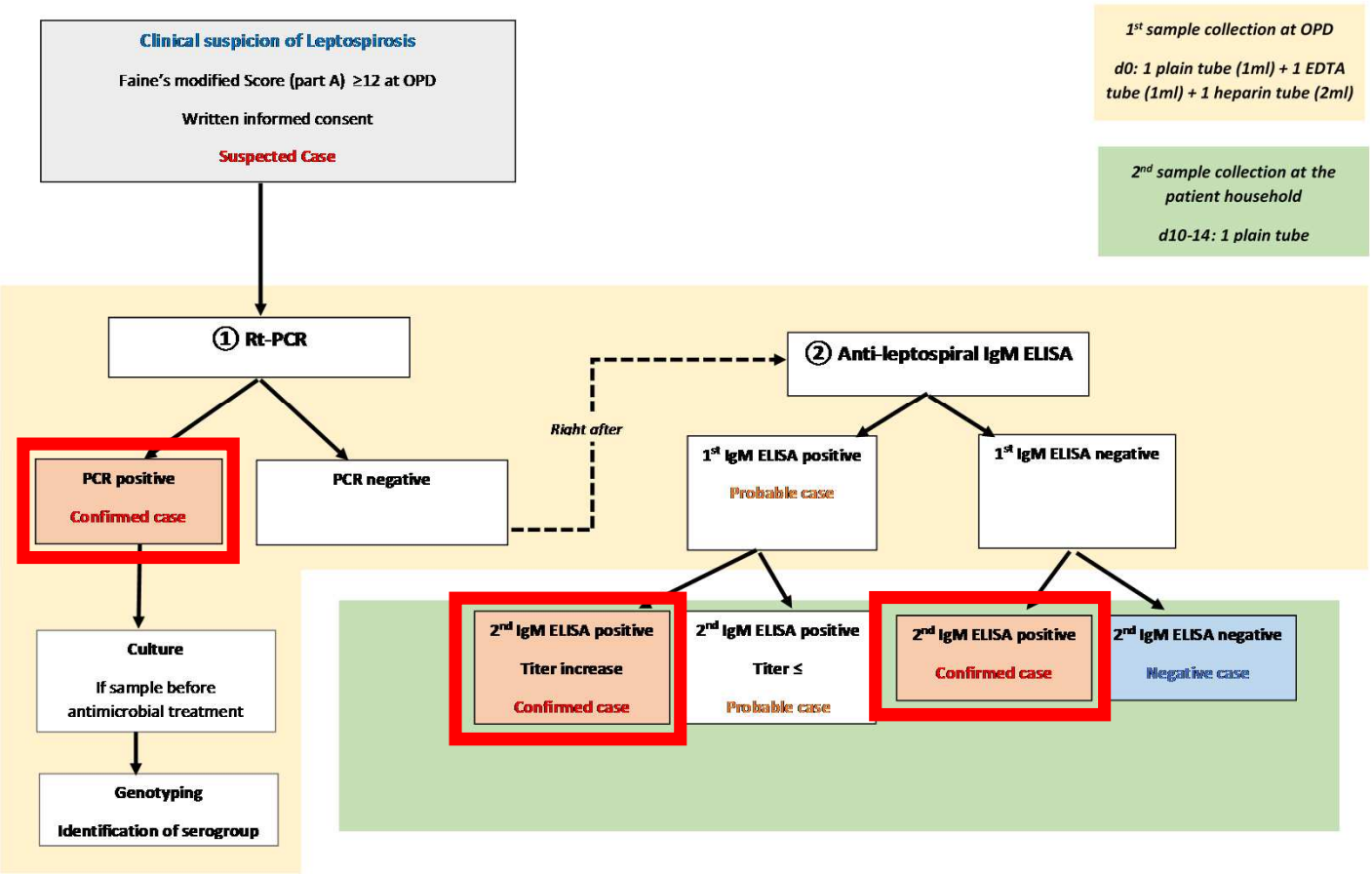
Part A, B and C score 25 or more

A score between 20 and 25 suggests a possible but unconfirmed diagnosis of leptospirosis

# Hospital based case-control study / CASE DEFINITIONS

- **Source population**: Patients attending OPDs from 9 selected public hospitals of Yangon region
- **Study population (cases and controls):** All clinically suspected patients from the source populations (**OPD** from 9 hospitals of Yangon region) during the study period.
- Suspected cases will be recruited **prospectively**.
- **Cases and controls** will be selected from suspected cases through a screening process (OPD) including leptospirosis confirmatory laboratory tests (NHL):
  - Confirmed Cases: **Cases** for the case-control study
  - Probable Cases
  - Non-leptospirosis (neither confirmed nor probable leptospirosis): **Controls** for the case-control study

# The hospital based case-control study / CASE DEFINITIONS




# Cases (confirmed)

= laboratory-confirmed suspected case

A suspected case with DNA from pathogenic *Leptospira* species detected by q-PCR into the acute-phase sample

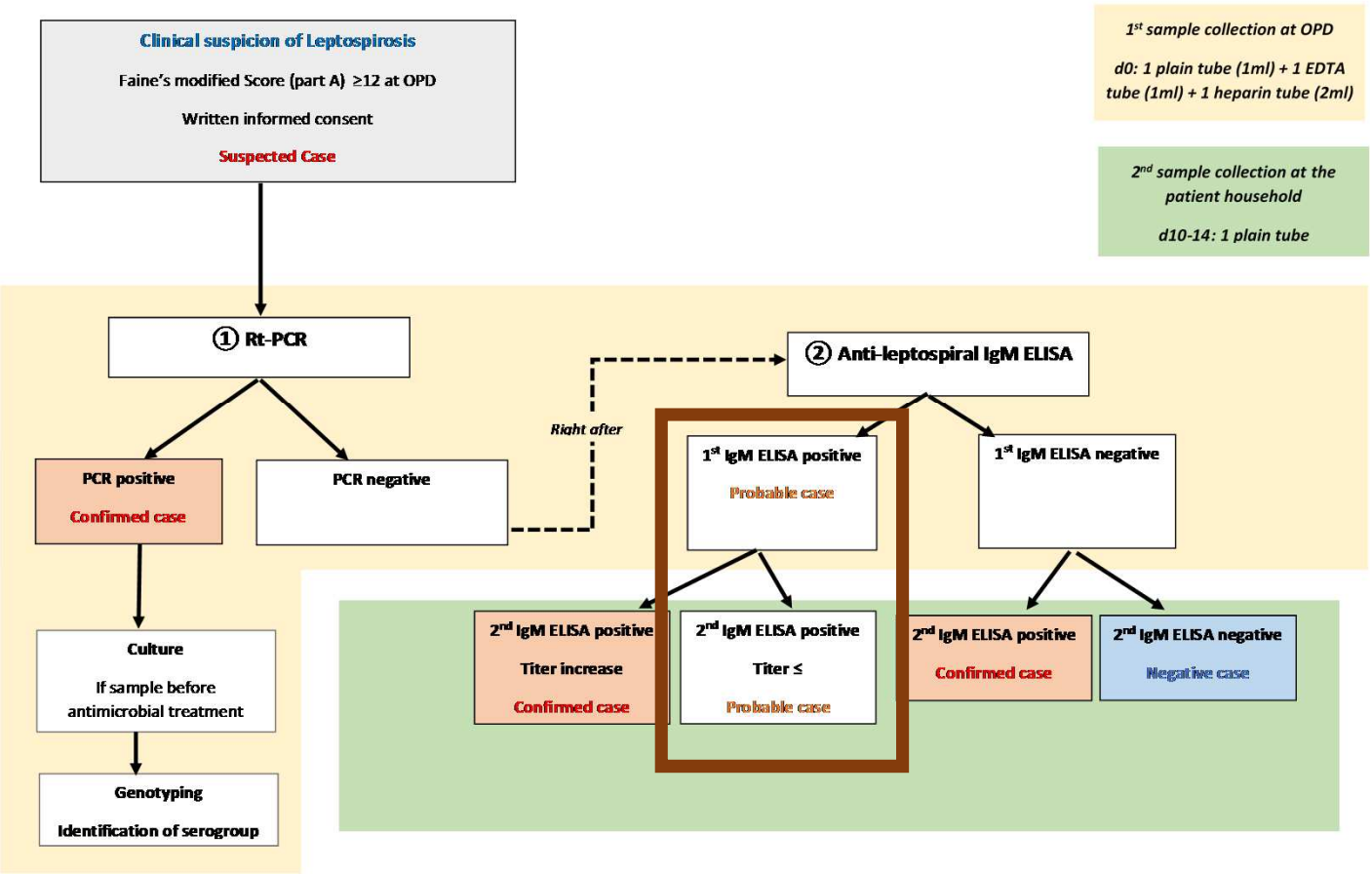
*Or*

A suspected case showing a seroconversion between the two consecutive anti-leptospiral IgM ELISA reaction on acute- and convalescent-phase samples

*Or*

A probable case showing an increase in titer between the two consecutive anti-leptospiral IgM ELISA reaction on acute- and convalescent-phase samples

# The hospital based case-control study / CASE DEFINITIONS



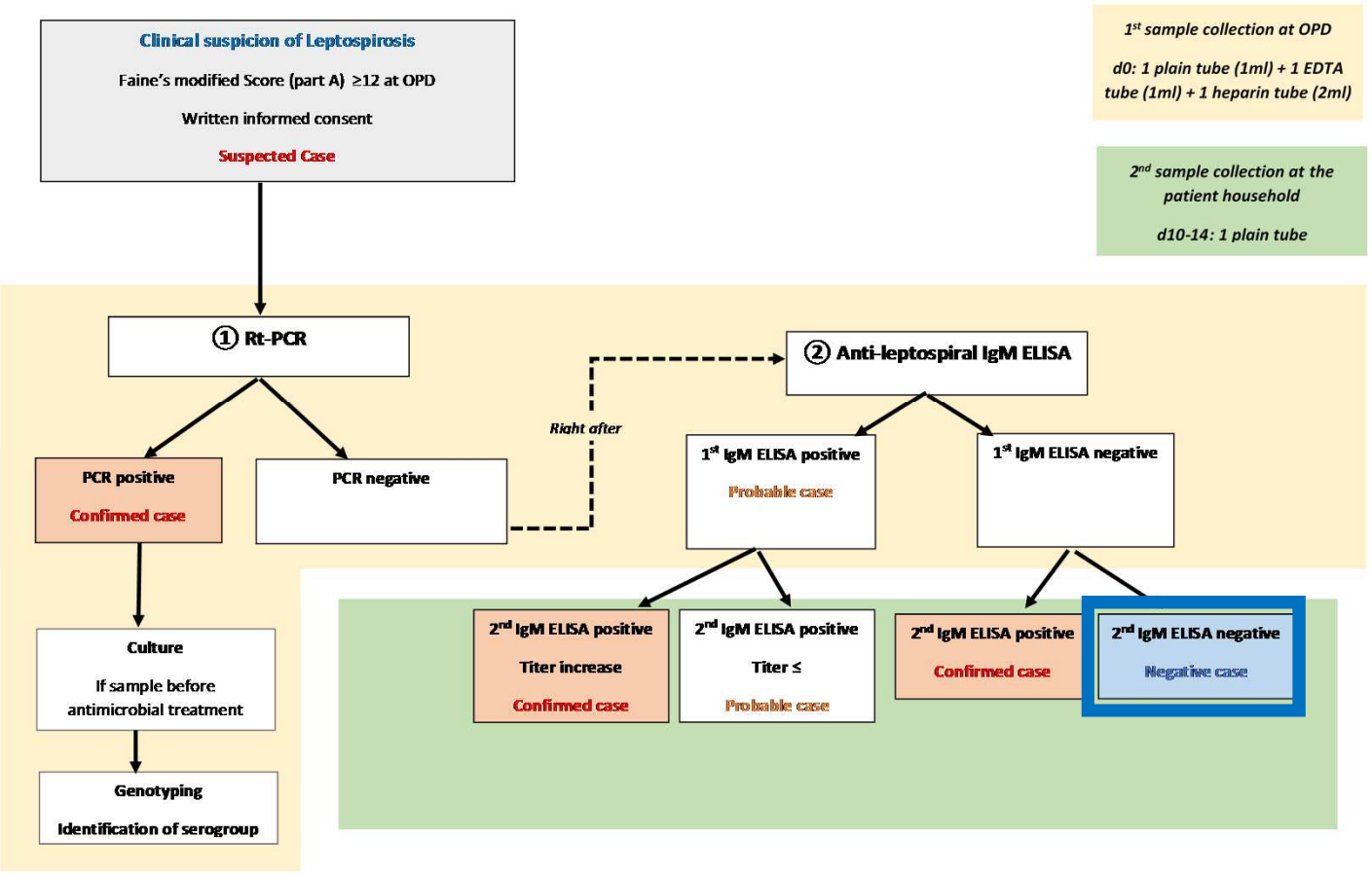

## Probable cases

A suspected case showing a negative result by q-PCR but a positive ELISA reaction into the acute-phase samples, pending for the convalescent-phase serum analysis by anti-leptospiral IgM ELISA reaction.

*Or*

A probable case at the acute-phase sample level and showing no increase in titer between the two consecutive anti-leptospiral IgM ELISA reaction on acute- and convalescent-phase samples.

# The hospital based case-control study / CASE DEFINITIONS




## Controls

= laboratory-negative suspected case

A suspected case showing a negative PCR and a double negative result at the two consecutive anti-leptospiral IgM ELISA reaction on acute- and convalescent-phase samples

# The hospital based case-control study / SAMPLE SIZE

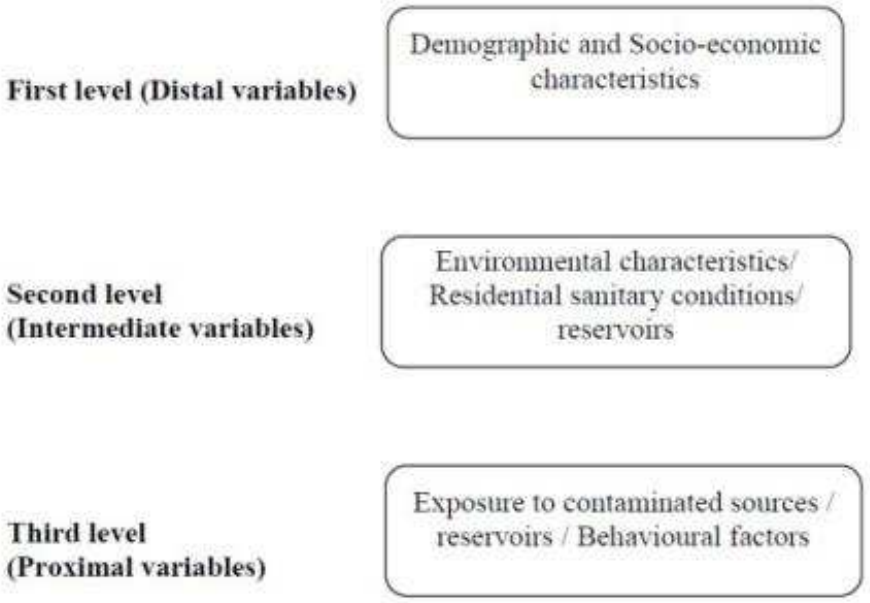
- A minimum sample of **280** laboratory-confirmed cases is required to detect an Odds Ratio of 2 for a risk factor (i.e. contact with contaminated water) present at an estimated 80% prevalence among non leptospirosis controls, with a 95% two sided confidence level and an 90% power for a case-control ratio 1:2 (1 case, 2 controls).
- Each case will be matched to two controls :
  - Age range: ±5 years AND
  - OPD of recruitment AND
  - Week of consultation

➔ **280 laboratory-confirmed cases matched with 560 controls**

- Budget allows for 4000 *suspected* cases ➔ 280 cases ? ➔ pilot study

# The hospital based case-control study / COVARIATES (Determinants)

***Hierarchical framework of possible determinants of leptospirosis***
(Agampodi et al., 2010)




Both individual-level and environmental determinants of leptospirosis are investigated

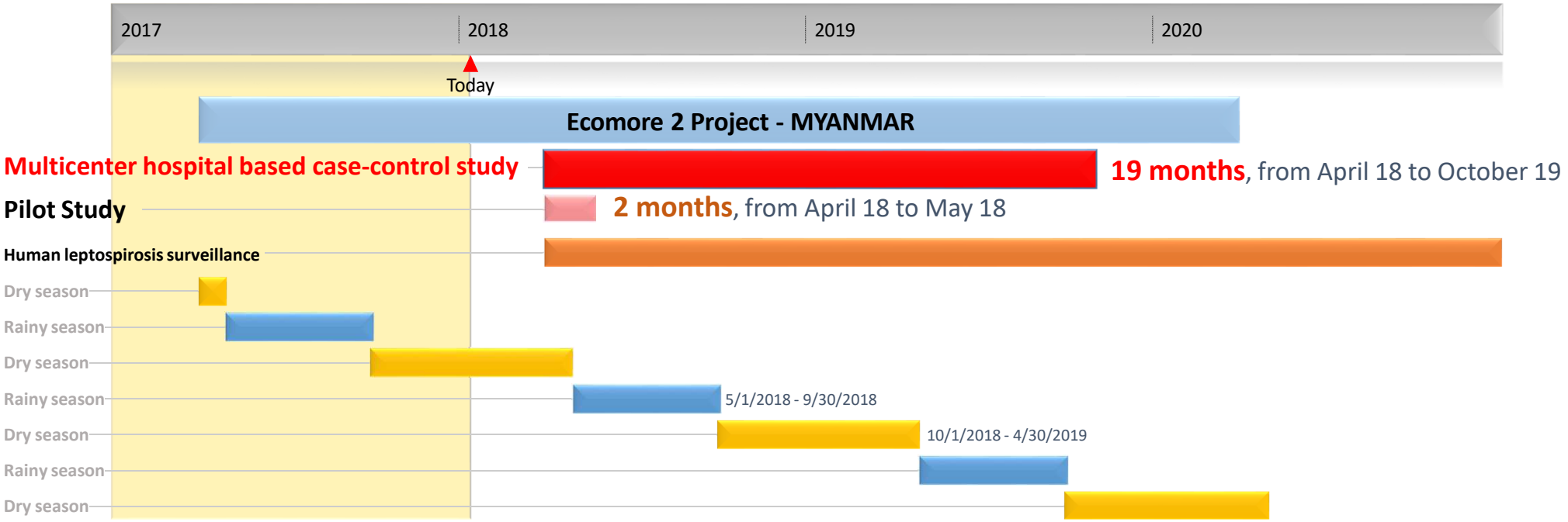
**Individual-level determinants** (demographic, socio-ecomomic and clinical variables) are investigated through interviews

**Environmental determinants** are investigated through interviews and household visit (spatial analysis)

Determinants are classified in a **conceptual hierarchical framework**

**Risk-factor analysis** with outcome measure: **odds ratio**

# Hospital based case-control study / STUDY SETTINGS




In **Yangon region**,

From **April 2018 to October 2019** included,

**9 selected public hospitals** in both urban and periurban areas,

One ward selected in each hospital: **the outpatient department** (OPD).

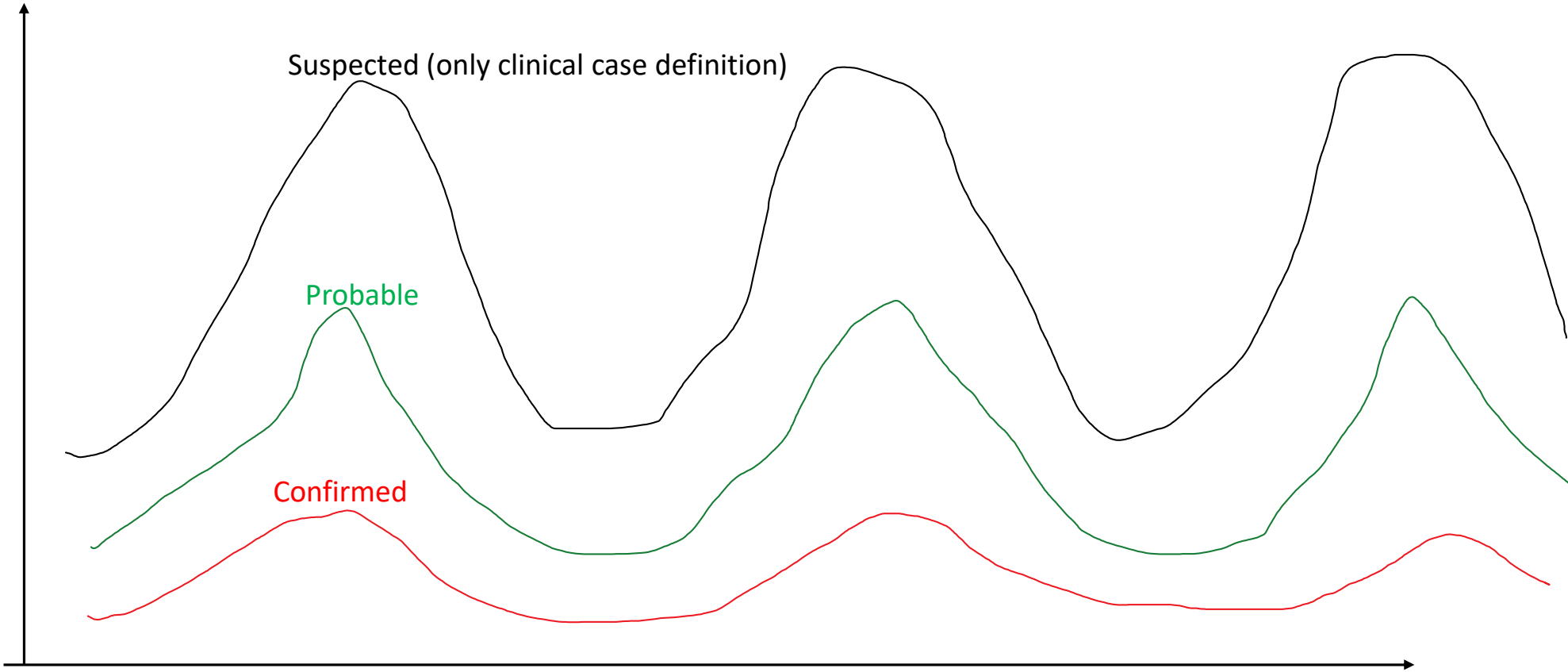
# The hospital based case-control study / EXPECTED OUTCOMES

Identify individual and environmental risk factors associated with human leptospirosis and provide appropriate recommendations for clinicians and at-risk population,

Estimate the leptospirosis burden in Myanmar and assisting the design of leptospirosis surveillance in Myanmar (proper and simple clinical case definition, focus surveillance on specific times in the year),

Build scientific collaboration with Epi-Unit of MoH in Naypidiaw (following the case one year after for study of long-term sequelae for example, or social impact of leptospirosis on the patient/family livelihood).

# The hospital based case-control study / A STEPPING STONE to LEPTO SURVEILLANCE



# The hospital based case-control study / DATA COLLECTION INSTRUMENTS

## Hospital – Outpatient department (d0)

| | |
|---|---|
| Screening in the waiting room | **Patient's digest** ✓<br>Informed Consent Form ◒ |

## Hospital – Outpatient department (d0-discharge)

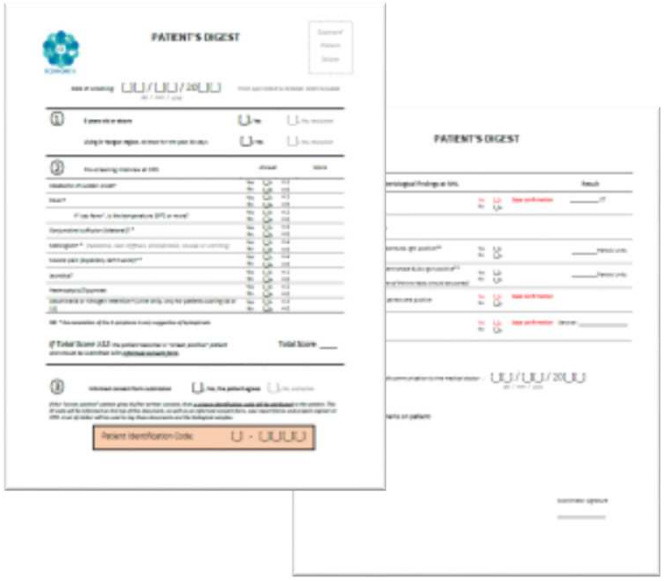
| | |
|---|---|
| Interview prior and during consultation or during the hospitalization | Case Report Form, part 1/2 ✓ |

## Patient's household (d10-d14)

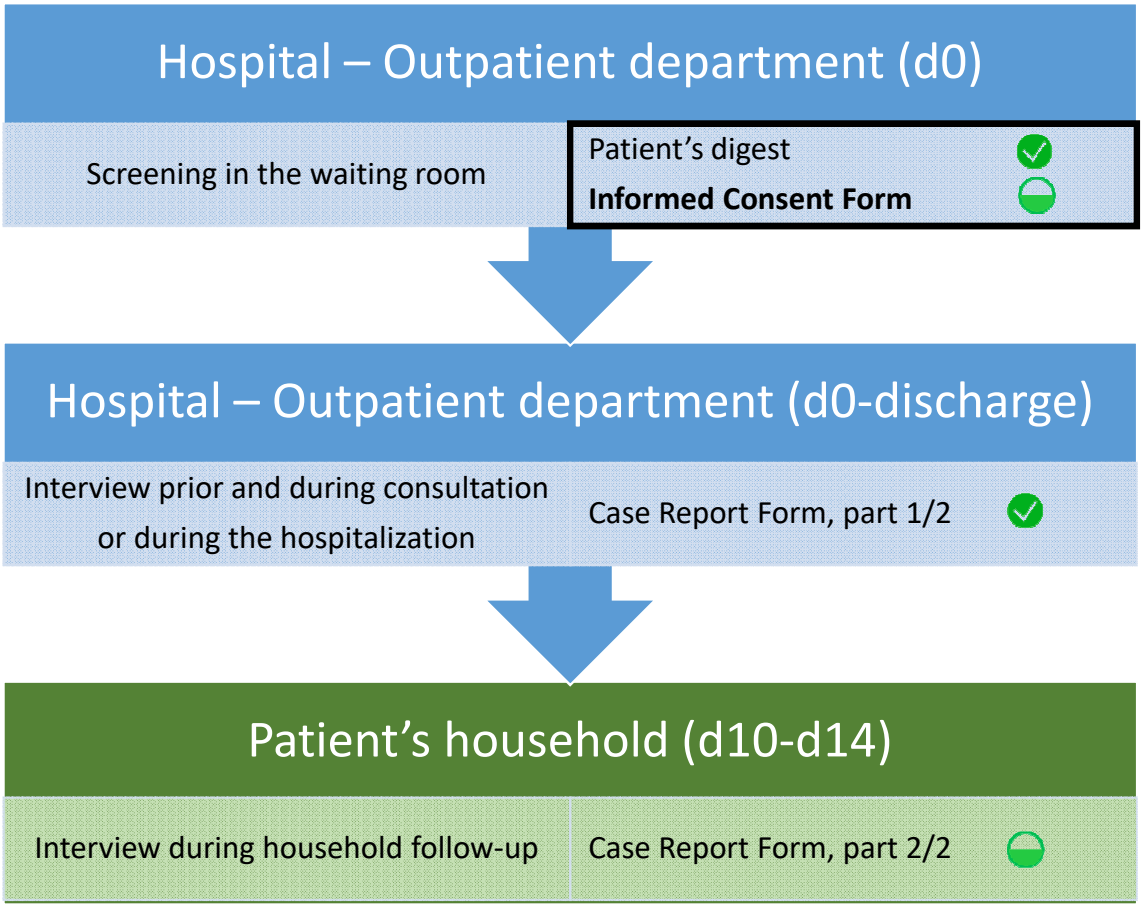
| | |
|---|---|
| Interview during household follow-up | Case Report Form, part 2/2 ◒ |

**Patient's digest**

Clinical cut-off score from the WHO Faine's criteria filled by a nurse/intern at OPD
Bacteriology results from the NHL filled by project coordinators



# The hospital based case-control study / DATA COLLECTION INSTRUMENTS




**Informed Consent Form**

Read by a dedicated nurse / intern
In patient's native language
Contact person: project coordinator (MD)
Written consent form

# The hospital based case-control study / DATA COLLECTION INSTRUMENTS

## Hospital – Outpatient department (d0)

| | |
|---|---|
| Screening in the waiting room | Patient's digest<br>Informed Consent Form |

## Hospital – Outpatient department (d0-discharge)

| | |
|---|---|
| Interview prior and during consultation or during the hospitalization | **Case Report Form, part 1/2** |

## Patient's household (d10-d14)

| | |
|---|---|
| Interview during household follow-up | Case Report Form, part 2/2 |

**Case Report Form, part 1/2**

Standardized questionnaire
8 Pages / 7 sections
Filled by nurses and medical doctors

# The hospital based case-control study / DATA COLLECTION INSTRUMENTS

## Hospital – Outpatient department (d0)

Screening in the waiting room

Patient's digest

Informed Consent Form

## Hospital – Outpatient department (d0-discharge)

Interview prior and during consultation or during the hospitalization

Case Report Form, part 1/2

## Patient's household (d10-d14)

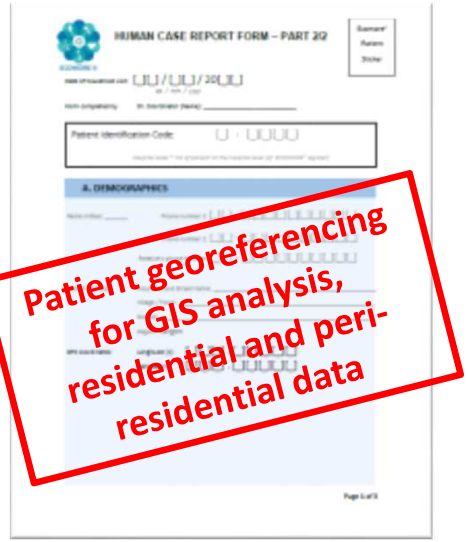
Interview during household follow-up

**Case Report Form, part 2/2**

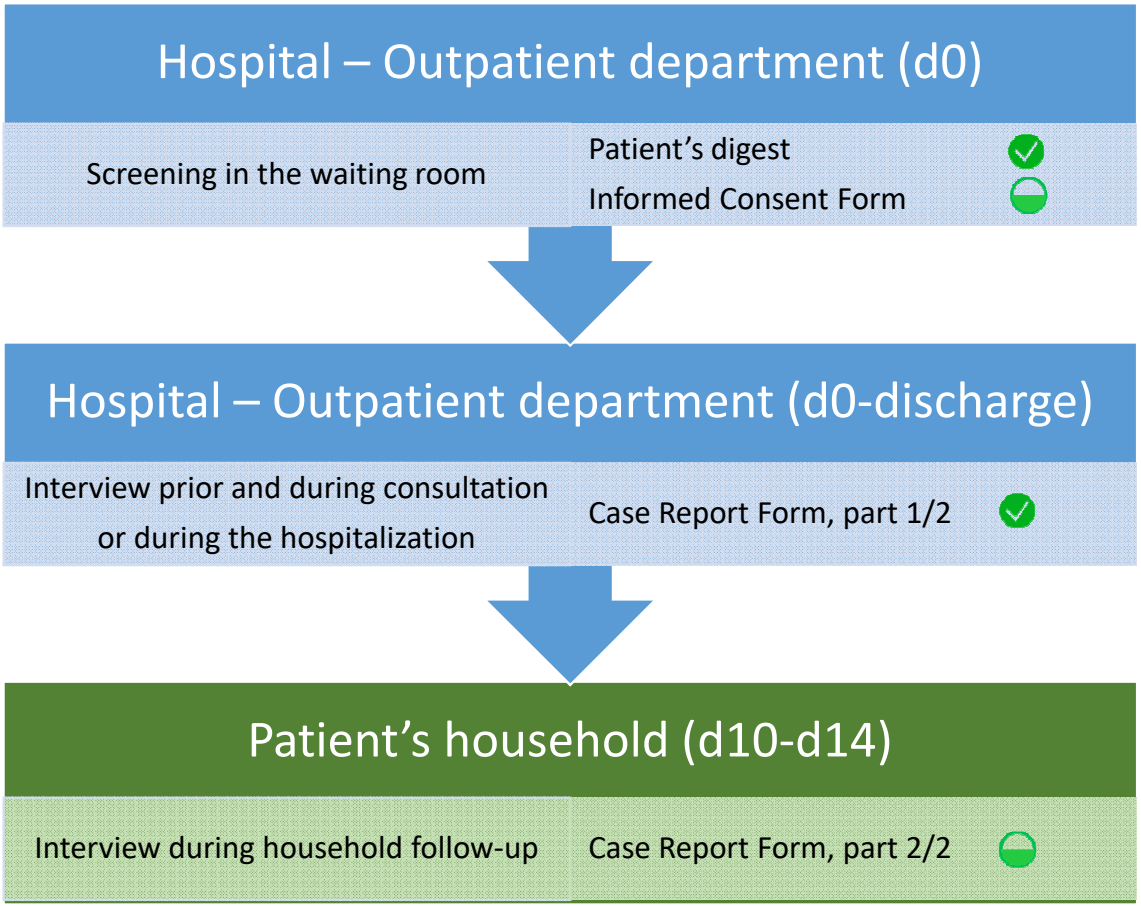
**Case Report Form, part 2/2**

Standardized questionnaire
3 Pages / 3 sections
Filled by the project coordinator

At this stage, one doesn't know who is case and who is control yet



# The hospital based case-control study / DATA COLLECTION INSTRUMENTS




*Data entry templates are:*

- designed to **fit the study needs** (RF analysis)
- **amenable to change** according to experts, clinicians, OPD staff during the pilot study

*Data will be:*

- collected by the project driver together with samples
- **checked** and **data entered** (Epi-Data 3.1) by the project coordinators and data managers

Statistical analysis (Stata or R) will be performed late 2019 by a dedicated biostatistician

# The hospital based case-control study / CHALLENGES AHEAD

The clinical presentation of leptospirosis is nonspecific and variable and we want to recruit both subacute and acute forms of leptospirosis;

Get acute AND convalescent sera from (some) recruited patients;

Feasibility of household investigations for each recruited patient;

Feasibility of matching (age, OPD, week) during case-control;

Ensure a constant involvement of hospital staff and a homogenous quality of data collected throughout the 19 months of study.

# The hospital based case-control study / A PROTOCOL STILL UNDER PROCESS

Consulting OPD staff and visiting OPDs will be decisive for the feasibility of the screening and recruitment at OPDs

For the screening in particular, consulting experts and local clinicians will be decisive for defining inclusion criteria, such as the cut-off score for screening patients at OPD (currently 12)

# Implementing a concurrent passive surveillance of leptospirosis among dogs

**Objectives**:

Monitor leptospirosis in time and space among dog population in Yangon region, involving private veterinarians (owned dogs), animal shelters (stray dogs) and the Veterinary Assay Laboratory (VAL) // human surveillance

Identify circulating serovars of pathogenic leptospires among canine population in Yangon region // human strains

Assess if dogs can act as sentinel for human leptospirosis in Yangon region (early warning system)

**Activities**:

Build capacity at the Veterinary Assay Laboratory level,

Enhance *One Health* collaboration and knowledge transfer between VAL and NHL,

Raise awareness about leptospirosis among veterinarians (Myanmar Veterinary Association) and issue recommendations.

# Acknowledgement

သင့်ရဲ့အာရုံစူးစိုက်မှုကိုမှုအတွက်ကျေးဇူးတင်ပါတယ်

Thanks for your attention

ຂອບໃຈ

Merci de votre attention

Salamat sa iyong pansin

Cám ơn các bạn đã chú ý lắng nghe

ស្តាប ់ អរគុ ណចំ ពោះ ការ យកចិ ត្តទុ កដាក់

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