

# **Tuberculosis infection in an Asian elephant at a Japanese Zoo and its first treatment in Japan**

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**Fukuyama Zoo, Hiroshima**

**October 22th, 2017**



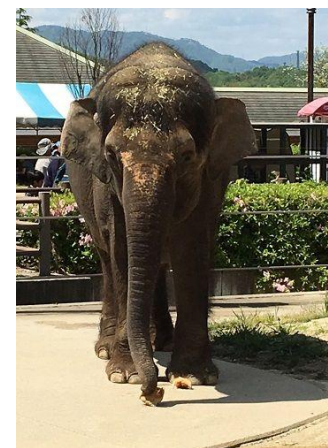
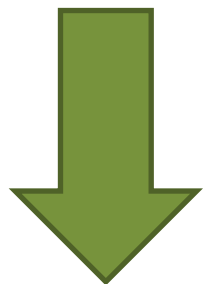
# Tuberculosis / TB

Infection with *Mycobacterium tuberculosis complex* (MTBC)

**In Human,**

- One of the top 10 causes of death worldwide
- Estimated 1/3 of world population are infected

**Infect wide variety of mammalian species**



**Most Important Disease for Conservation Medicine**

# TB in Elephants

## Worldwide

Reported in domestic, Zoo, and free-ranging elephants

Local prevalence rate (Most of them are sero-prevalence)

- India : 15.2% (Abraham, 2008)
- Nepal : 15.6% (Mikota et al., 2007)
- Peninsular Malaysia : 20.4% (Ong et al., 2013)
- USA : estimated 12.4% (Mikota et al., 2015)

**Every elephants in the world can be infected**

## In Japan

Old 2 cases were reported

- 1959 Kagoshima (Kawahara et al., 1962)
- 1962 Nagoya (Chiba, 1993)

**Diagnosed at postmortem  
and  
Had not received any TB  
treatment**

# Fukuyama Zoo

- Located in Fukuyama (Hiroshima prefecture)
- Keeps 66 species 363 individuals
- Approximately 300,000 visitors in one year





# Patient

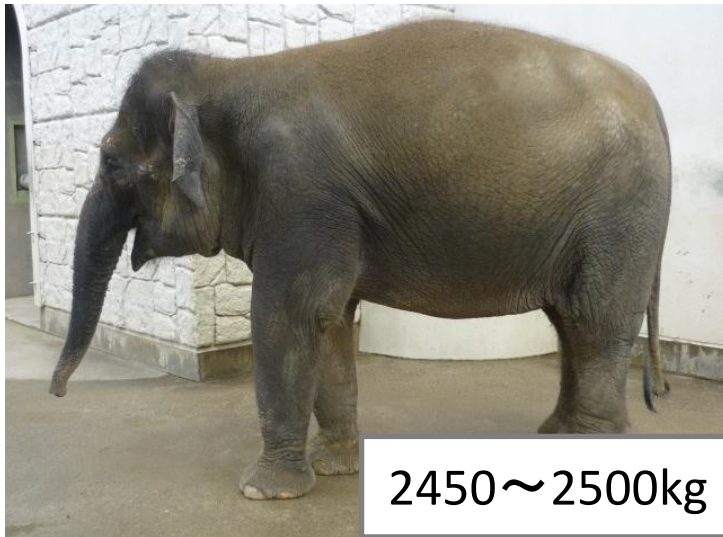
- Borneo Elephant  
(*Elephas maximus borneensis*)
- Female
- Estimated 17 years old



**Fuku-chan**

# Clinical Signs

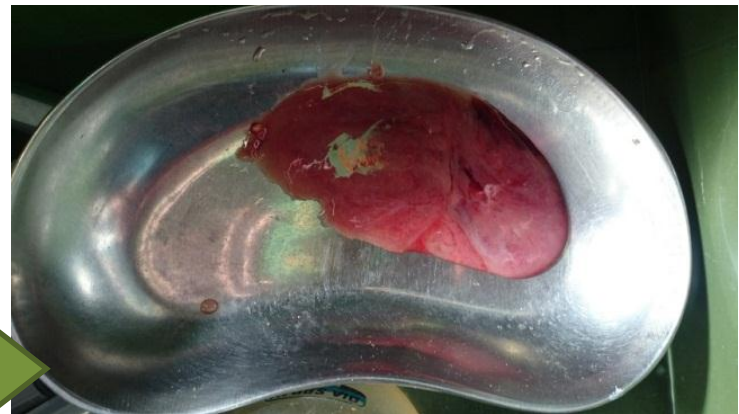
- Chronic anorexia and Weight loss



Sep,2015  
To  
Feb,2016



- Slight fever
- Sporadic coughing
- **Vaginal discharges**



# Empiric Treatment

- A/G ratio : 0.35 ↓
- WBC : 29,700 ↑



**Suspected  
Bacteremia  
(Including TB)**

Cefazolin IV or Ofloxacin PO total 3weeks

Piperacillin IV/IM

Isoniazid (only) IV/rectally } 2weeks

# Diagnosis

March 5<sup>th</sup>, 2016

Sputum (“phlegm”) with coughed up were expectorated



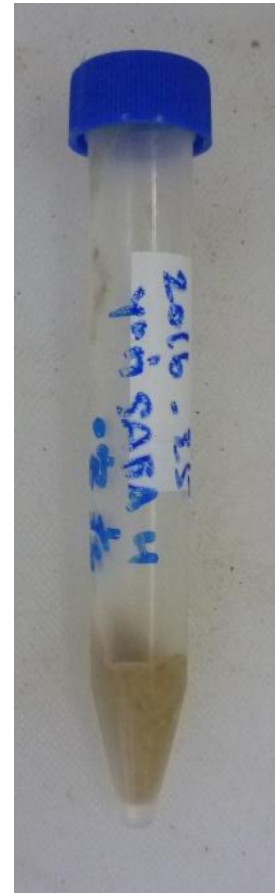
March 9<sup>th</sup>, 2016

DNA in TB bacteria were detected  
by PCR and LAMP (Loop mediated isothermal amplification)



At a later date

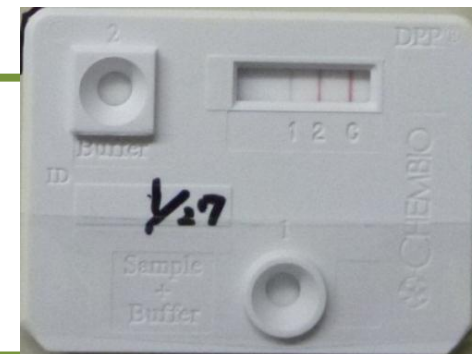
Mycobacterial strain was isolated  
and identified as MTBC by multiplex PCR.



Rapid Serological Test

(Chembio DPP® VetTB Assay for Elephants)

**The serum sampled in 2003 was positive.**





# Results of Microbiological Tests

Sample	Fluorescence method	PCR	LAMP	Culture
Sputa	+	+	+	+
Feces	+	+		+
Urines	±	+		+
Vaginal discharges	+	+		+
Trunk washes	+	+		-



## Diagnosed as “Miliary TB”

TB bacteria travel through the bloodstream and spread throughout the body

# The 1<sup>st</sup> Regimen

Oral plans were failed ➡ Administered 3 drugs rectally

1.



1. Isoniazid(INH)

2.



2. Pyrazinamide(PZA)

3.



3. Levofloxacin(LVFX)



Can be administered both **orally** and **rectally** in elephants (USAHA, 2012)



Few reports of **rectal** administration in elephants

In Beagle Dogs,  
Absorbed with rectal administration  
(Japanese pharmaceutical company., Personal Communication)

# Rectal Administration



**Dissolved in warm water**



**Nasal tube for cattle**





**Remove rectal feces**



**Liquid drugs were thrown in**

**Continued for over 6 months**

# Progress of the 1<sup>st</sup> Regimen

- Body weight      2205kg            2470kg
  - Vaginal discharges
  - Expectoration of sputa
  - Slight fever
-  **Disappeared**

**However**

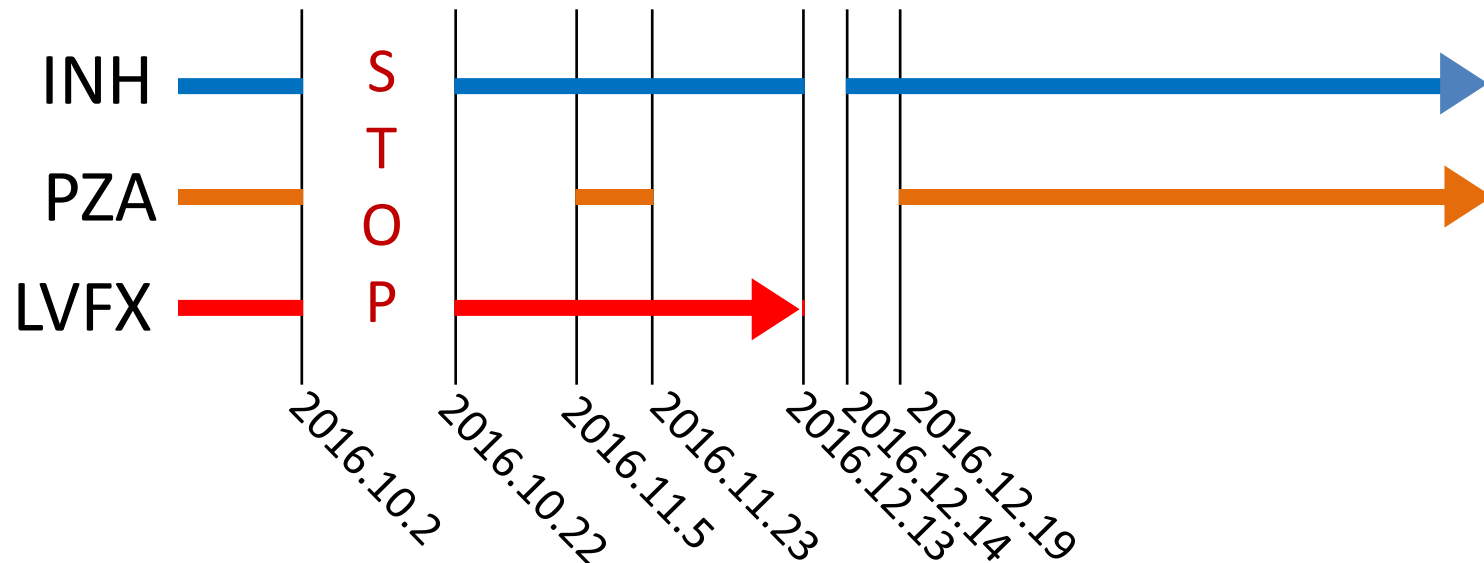
After 6 months of treatment (in September),

**Serious side effects appeared unexpectedly**

Acute Anorexia, Constipation and Colic

# Side Effect Management

All anti-TB drugs were stopped for 3 weeks.  
And the regimen was changed many times.



Could not identify the drug which caused side effects.



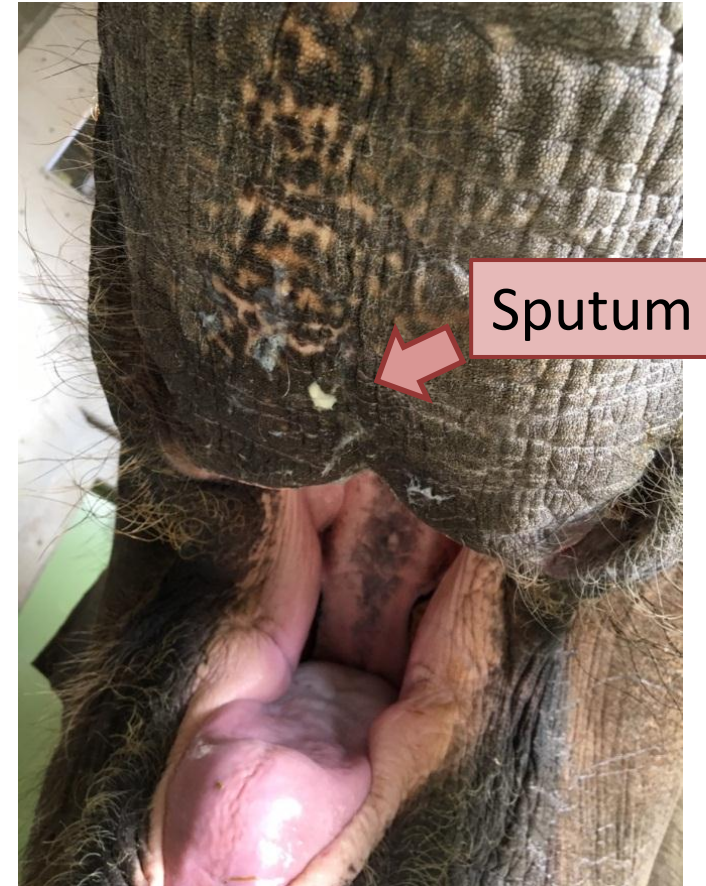
# Isolation of INH Resistant Bacteria

## 9 months after the diagnosis

The elephant started to expectorate sputa again.

## 12 months after the diagnosis

INH resistant TB bacteria was isolated.



**New regimen was required.**

# The 2<sup>nd</sup> Regimen

INH **X**

PZA

LVFX



1. PZA

2. LVFX

3. Ethambutol(EB)

4. Rifampicin(RFP)

3.



4.



**EB** : Cause rectal irritation and be quickly expelled  
( Maslow et al., 2005)



**Has not occurred in this case**

**RFP** : Not to be absorbed with rectal administration  
(Brock et al., 2014)



**Required to be administered orally**

# Oral Administration with Molasses Balls



- RFP powder



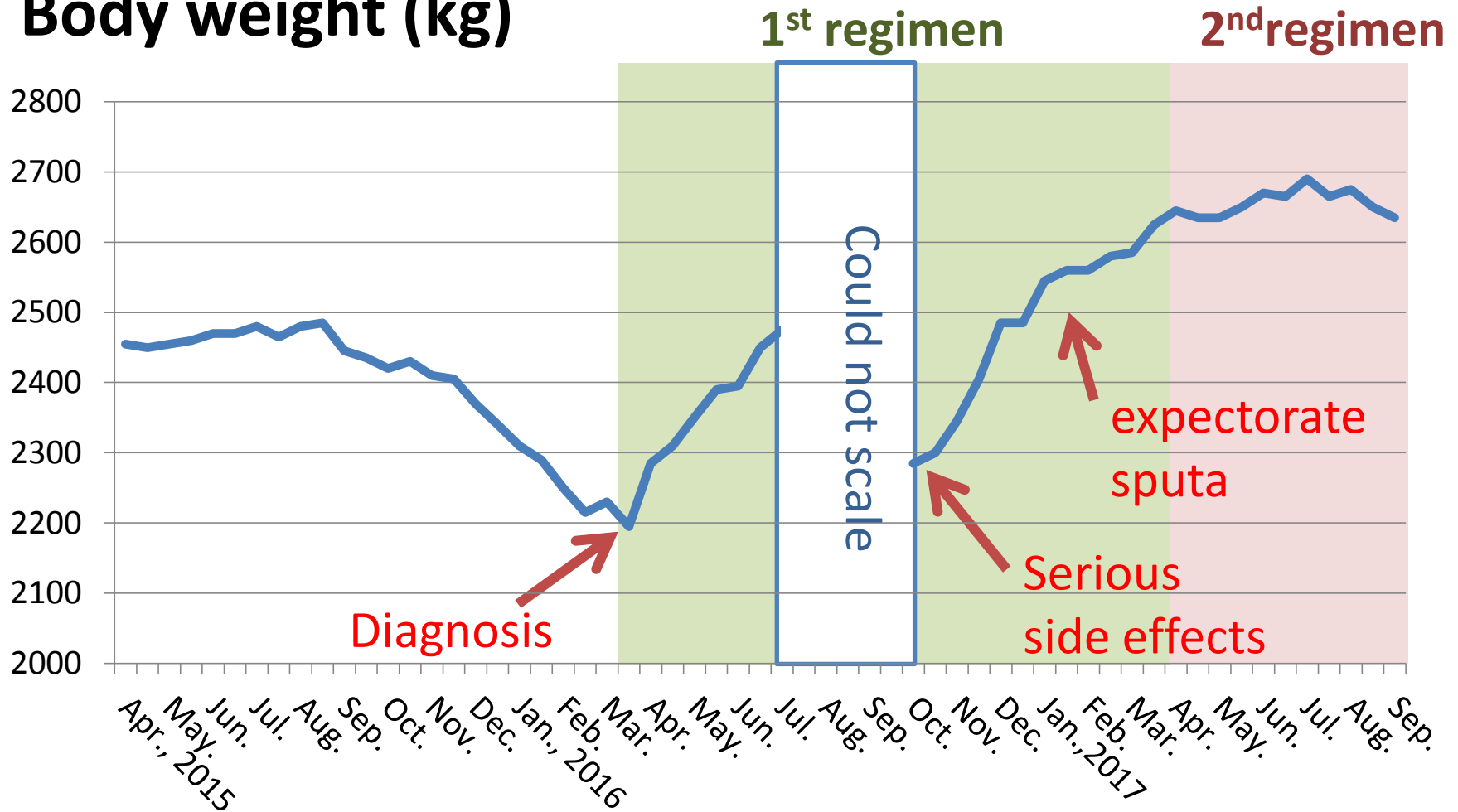
- Liquid molasses
- Flour



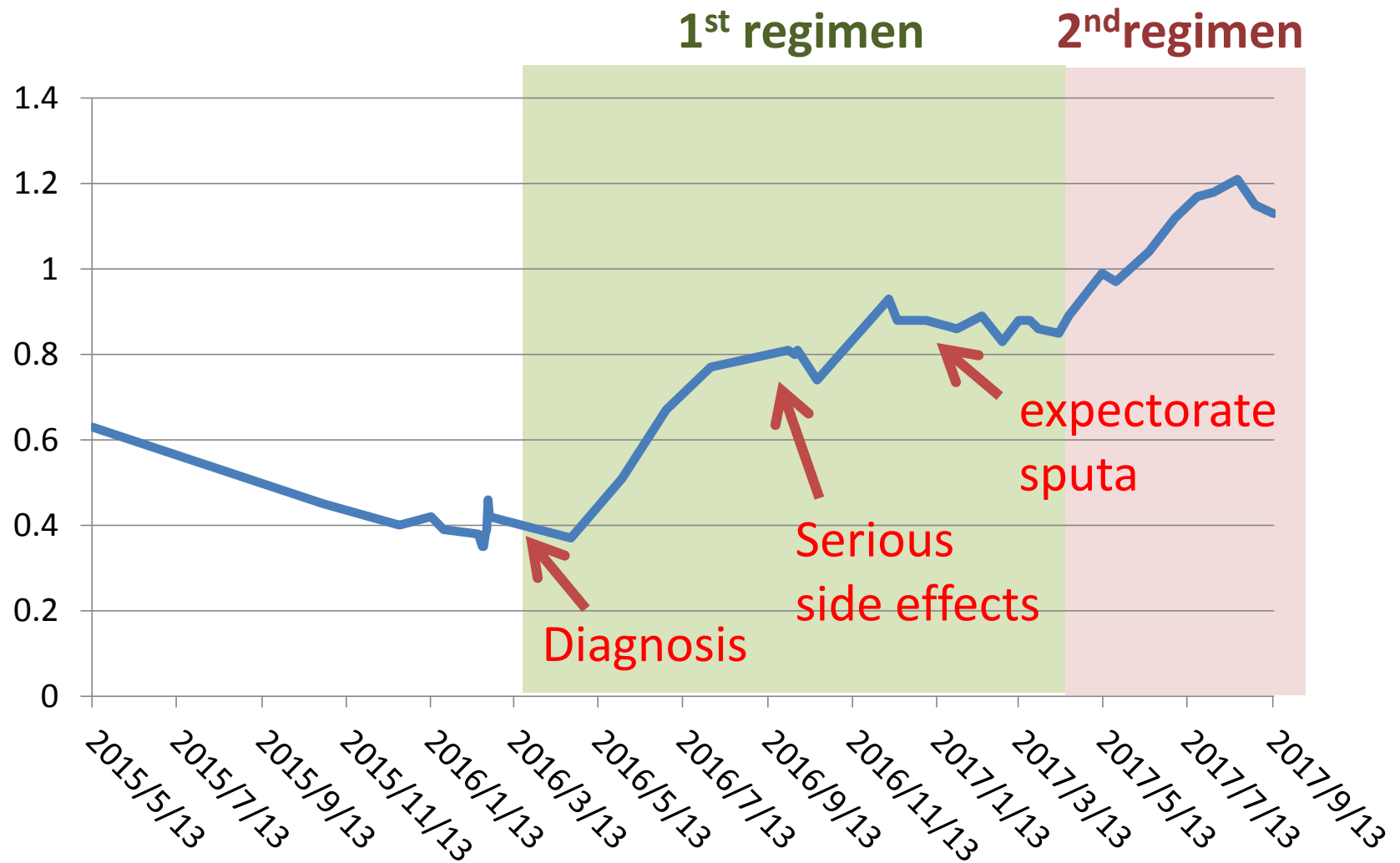
**Has been continued  
till today  
(over 6 months )  
And need to be  
continued more 1 year**

# Progress

## Body weight (kg)



# A/G Ratio





# Side Effects of the 2<sup>nd</sup> Regimen

## During all that time of the 2<sup>nd</sup> regimen

- Mild anorexia
- Increase of total bilirubin and total bile acid  
0.1 → 0.6                      6.0 → 64.6

## In September

- Mild constipation and colic (Only one day)

**Same month as serious side effects in the 1<sup>st</sup> regimen**

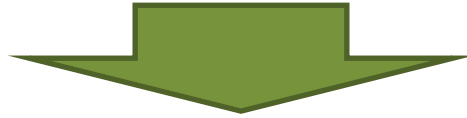
**Serious side effects have not occurred.**

# Discussions and Conclusions



# Serological Test

**The serum sampled in 2003 (kept in a freezer) was positive for TB by rapid serological test.**



**While it was thought that there was no elephant TB in Japan...**

**At least, this elephant has been infected with TB for over 14 years unnoticed.**

# Follow up

In human TB, **X-ray and CT** are common methods of “follow-up”.

**Commonly impossible in elephants**



**A/G ratio can be useful in elephants.**

# Side Effects

Anorexia and hepatopathy → Common in elephant TB

Constipation and Colic → Few reports

[ In this case, the drug which caused **constipation and colic** was not identified. ]

They occurred **acutely in September** with both the 1<sup>st</sup> and the 2<sup>nd</sup> regimen (Severities were quite different).

## September in Japan

- Beginning of autumn
- Air temperature drops
- Start drying

## The change of patient in Sep.

Intake of oat hay increased

**These seasonal changes might be associated to occurrence of the side effects.**



# Administration

**Rectal administration** is useful when the elephant does not accept oral administration.

However, only a few drugs were reported to be absorbed.

**This case is more likely to be committed to a favorable outcome by the 2<sup>nd</sup> regimen including LVFX.**

## LVFX (WHO, 2011)

- One of the “fluoroquinolones”
- Has strong anti-TB activity
- Be administered for human cases with drug resistance or serious side effects

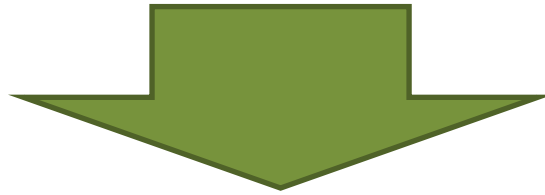


**The multiple-drug therapy with LVFX  
might be effective in elephant TB (including miliary TB).**

# Current Situation and Future Plan

Body weight : 2710kg (October 21<sup>st</sup>, 2017)

Fortunately, “The 2<sup>nd</sup> regimen” has been continued until today without serious side effects.



We think this regimen should be continued at least another 1 year (total 18 months).

# Acknowledgement

We would like to express the deepest appreciation to a lot of people who helped us very kindly.

Fukuyama Zoo





**Thank you very much**