INA RESPOND
INDONESIA RESEARCH PARTNERSHIP ON INFECTIOUS DISEASE

The Etiology of Acute Febrile Illness Requiring Hospitalization (AFIRE)

Version 6.0, 31 December 2014

INA-RESPOND Annual Meeting
Jakarta, 30 April 2015

Background

- Acute Febrile Illness: approximately 20-25% of hospitalizations in Indonesia and present a major cause of morbidity and mortality
- In developing countries, a clinical presentation with fever is usually linked to an infectious etiology
- Mostly clinical diagnoses only → inappropriate clinical management
- Large-scale studies to identify causes of febrile illnesses in Indonesia have not been conducted

Background

- Most studies were designed to identify for specific agents and did not collect clinical data, outcomes and etiologies to measure disease burden systematically

- This study is designed to provide data that represents the clinical profile of infectious diseases in several large hospitals by conducting a study to record clinical data and to identify the etiologies of fever

Research Question

- What are the etiological “infectious” agents of acute febrile illnesses in patients requiring hospitalization?

Potential Research Benefits

- Identifying etiologies of fever
- Improving patient diagnosis and management
- Identifying novel agents → public health policy
- Generating other research questions

Study objectives

Primary

- To identify the etiology of acute febrile illness cases and evaluate clinical manifestations and outcomes

Study Objectives

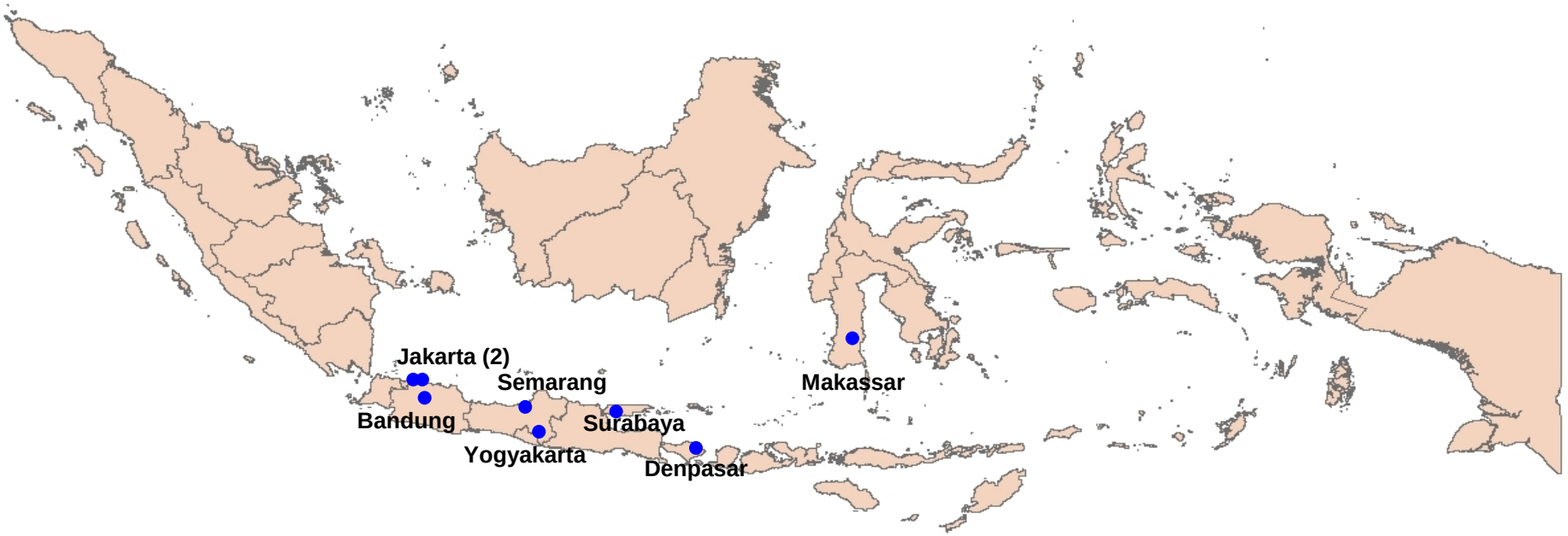
Secondary

- To provide clinical data for improving and/or developing clinical management and health policies
- To enhance research capacity and networking for infectious diseases in Indonesia
- To establish a repository of biological specimens for future studies

Research Methods

a. Sites

Eight hospitals, network members



- RSUP dr Hasan Sadikin, Bandung
- RSUP Sanglah, Denpasar
- RSUPN dr Cipto Mangkusumo, Jakarta
- RSPI Prof dr Sulianti Saroso, Jakarta
- RSUP dr Wahidin Sudirohusodo, Makassar
- RSUP dr Kariadi, Semarang
- RSUD dr Soetomo, Surabaya
- RSUP dr Sardjito, Yogyakarta

Research Methods

b. Type and design

- Hospital-based study without treatment intervention
- Hypothesis-generating cohort study

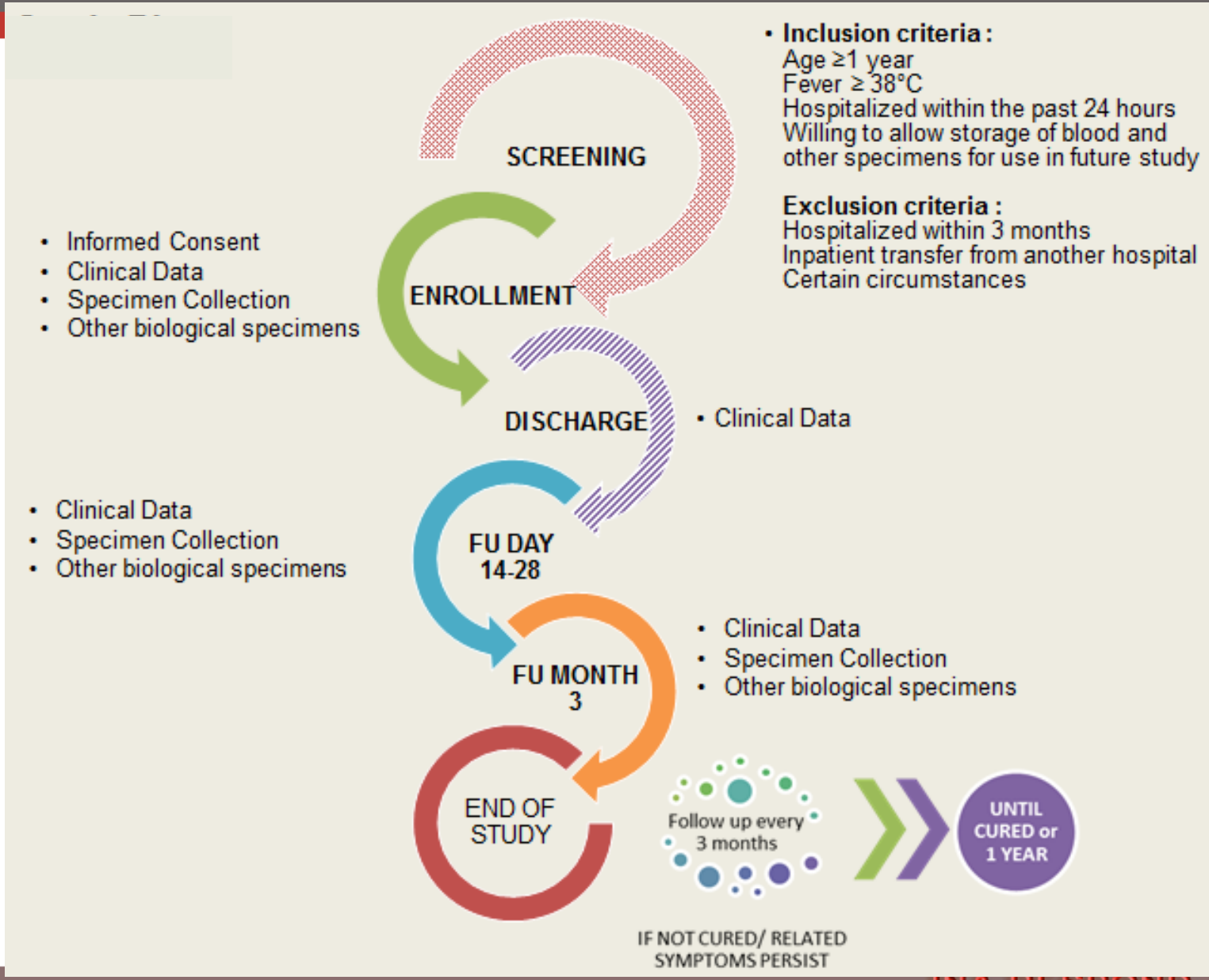
c. Sample size

- Sample size: Total 1600 subjects, max 3200 subjects based on interim analysis*

*Interim analysis: at several points following initiation of enrollment

Research Methods

d. Study Plan



Preliminary Results

Site Activation Status

Site number	Activation status date	First enrolled Subject Date
520 – Denpasar	Jul 16, 2013	Jul 18, 2013
560 – Semarang	Aug 12, 2013	Aug 22, 2013
580 - Yogyakarta	Aug 14, 2013	Aug 28, 2013
510 – Bandung	Sept 04, 2013	Sept 05, 2013
550 – Makassar	Oct 04, 2013	Oct 16, 2013
570 – Surabaya	Dec 27, 2013	Jan 03, 2014
530 – Jakarta (RSCM)	Nov 06, 2014	Nov 27, 2014
540 – Jakarta (RSPI-SS)	Nov 17, 2014	Dec 08, 2014

Estimation of study duration

Target Population : 1600 subjects

Until 12 Apr 2015 : 945 subjects enrolled

Average of network enrollment from the last 6 month :52

Months to go to reach 1600 subjects: 655:52 **= 12.6 months**

Data Interim Analysis (n=635)

4-5 Feb 2015

Subject's General Characteristics (n=635)

Variable	Pediatric		Adult ≥ 18 y.o (n=386)
	<5 y.o (n=85)	5 - <18 y.o (n=164)	
Demography			
Male (n=347)	44	86	217
Female (n=288)	41	78	169
Age (Median, range) years old	2 (1-4) y.o	11 (5-17) y.o	35 (18-98) y.o
Mortality			
Outside hospital (n=15)			
- < 1 month after discharge (n=8)	0	1 (0.6%)	7 (1.8%)
- ≥ 1 month after discharge (n=7)	2 (2.3%)	0	5 (1.3%)
During hospitalization (n=22)	3(3.5%)	2(1.2%)	17 (4.4 %)

Onset and Duration

Variable	Pediatric		Adult ≥ 18 y.o (n=386)
	<5 y.o (n=85)	5 - <18 y.o (n= 164)	
Onset of fever – hospital admission day (median, range)	3 (1-21) days	5 (1-36) days	5 (1-32) days
Length of hospitalization (median, range)	5 (6-20) days	6 (2-54) days	6 (1-51) days
ICU			
Yes (n=18)	5 (5.8%)	4 (2.4 %)	9 (2.3%)
Death (n=14)	2	4	8
Alive (n=4)	3	0	1
Length of stay in the ICU (median, range)	5 (4-8) days	5 (3-48 days)	5 (1-17) days

Antibiotic use

Antibiotics given Prior to Hospital	Pediatric		Adult ≥ 18 y.o
	<5 y.o	5 - <18 y.o	
Prior to hospital			
Yes (n=			.9%)
No (n=			.5%)
Unkno			6%)
Most Anti			(28/69)
			n (8/69)
			(7/69)
			(5/69)
			col (5/69)
			n (5/69)

A Before			18 y.o
Before Blo Hospital			
Yes (n=2			.3%)
No (n=3			.7%)
Most Anti			(75/171)
			(38/171)
	Cefotaxim (3/41)	Chloramphenicol (7/51)	Cefotaxime (16/171)
	Amoxicillin (2/41)	Cefotaxim (4/51)	Cotrimoxazole (5/171)
	Ampicillin + Gentamycin (2/41)	Ampicillin + Gentamycin (3/51)	Levofloxacin (4/171)
		Ciprofloxacin (4/51)	
		Ampicillin + Gentamycin (3/51	

26% patients received pre-hospital antibiotic treatment

(*56% no antibiotics; 18% unknown*)

44% patients received antibiotics before blood cultures

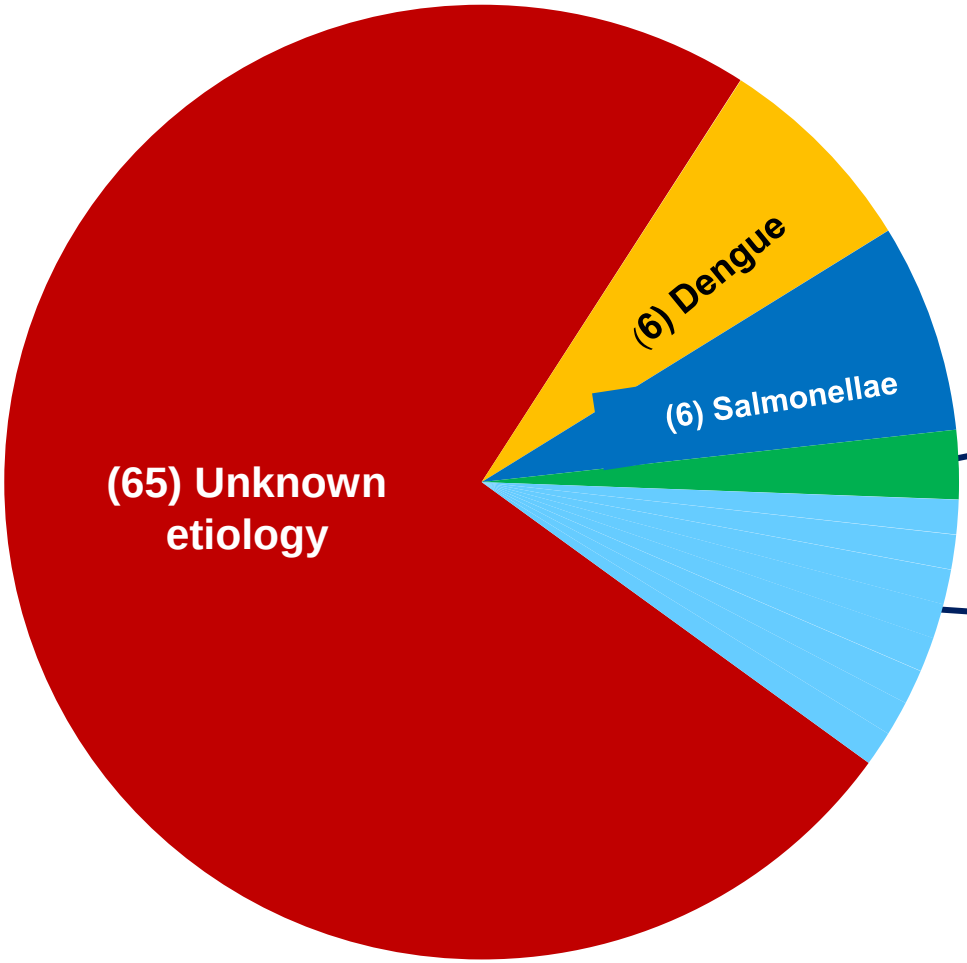
Etiology of AFI

- The etiology of acute febrile illness were identified in 202 (52.3%) subjects.

- The majority were diagnosed by
  - serological assays (65.3%)
  - culture non-blood specimens (10.3%)
  - microscopic (5.6%)
  - blood culture (3.8%)
  - Antigen detection (3.8%)
  - Serological assay+ blood culture (3.3%)
  - Other combination (7.5%)

- The predominant were :
  - Salmonellae (S. typhi/paratyphi): 88 (43.6%)
  - Dengue : 64 (31.7%)
  - Leptospira sp : 16 (7.9%)

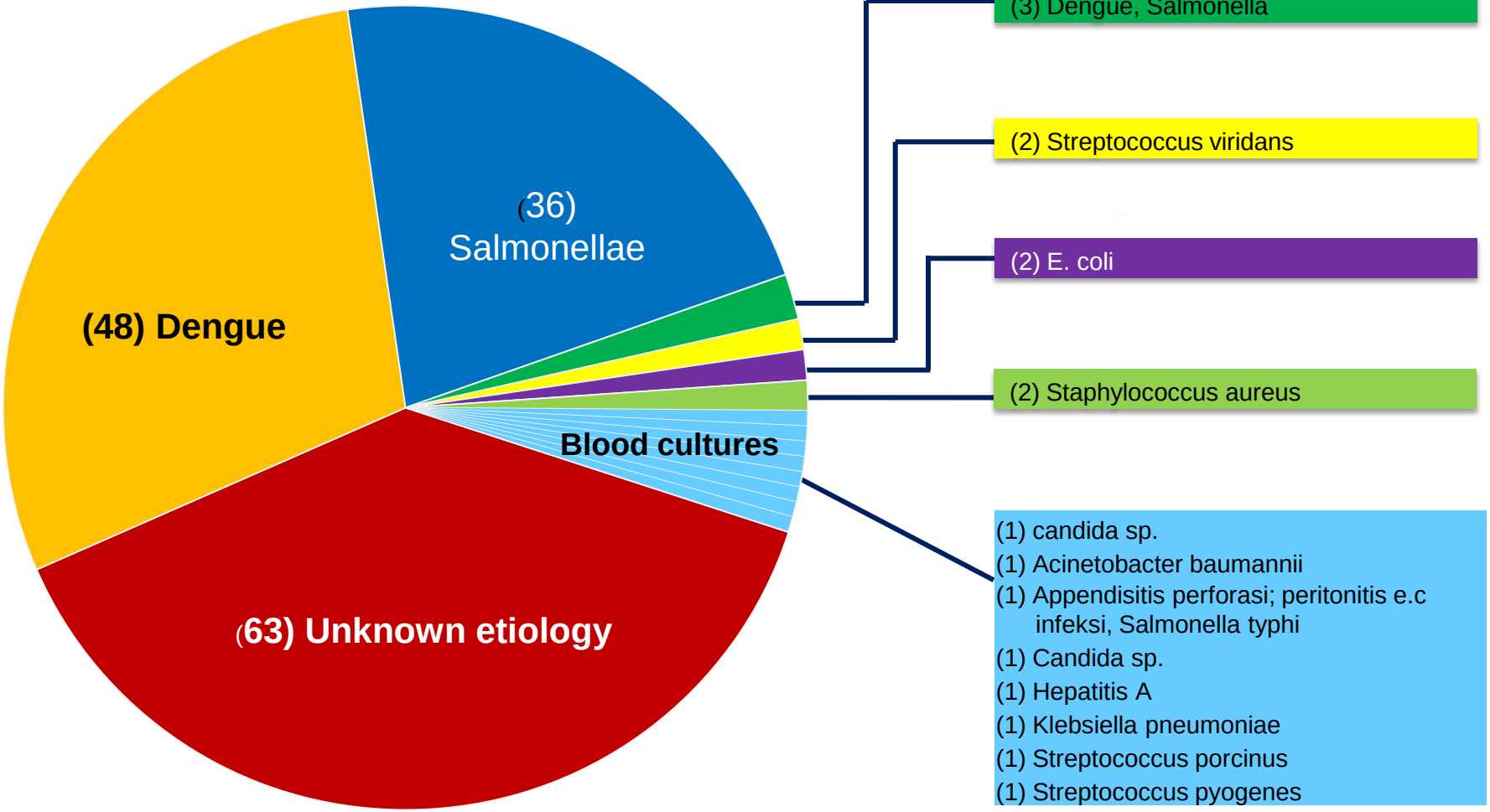
Etiological Diagnoses - 1- 4 y.o (n=85)



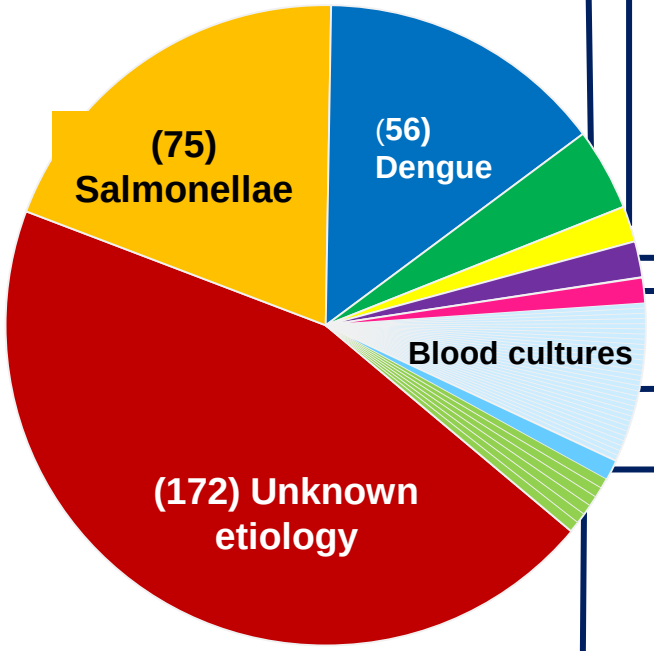
(2) Streptococcus viridans

(1) CMV
(1) E. Coli
(1) E. coli serotype III
(1) Klebsiella pneumoniae ssp pneumoniae
(1) Pseudomonas aeruginosa
(1) Staphylococcus hominis

Etiological Diagnoses – 5 - 17 y.o (n=164)



Etiological Diagnoses - >17 y.o (n=386)



(7) Dengue, Salmonella

(16) *Leptospira sp*

(7) M. tuberculosis

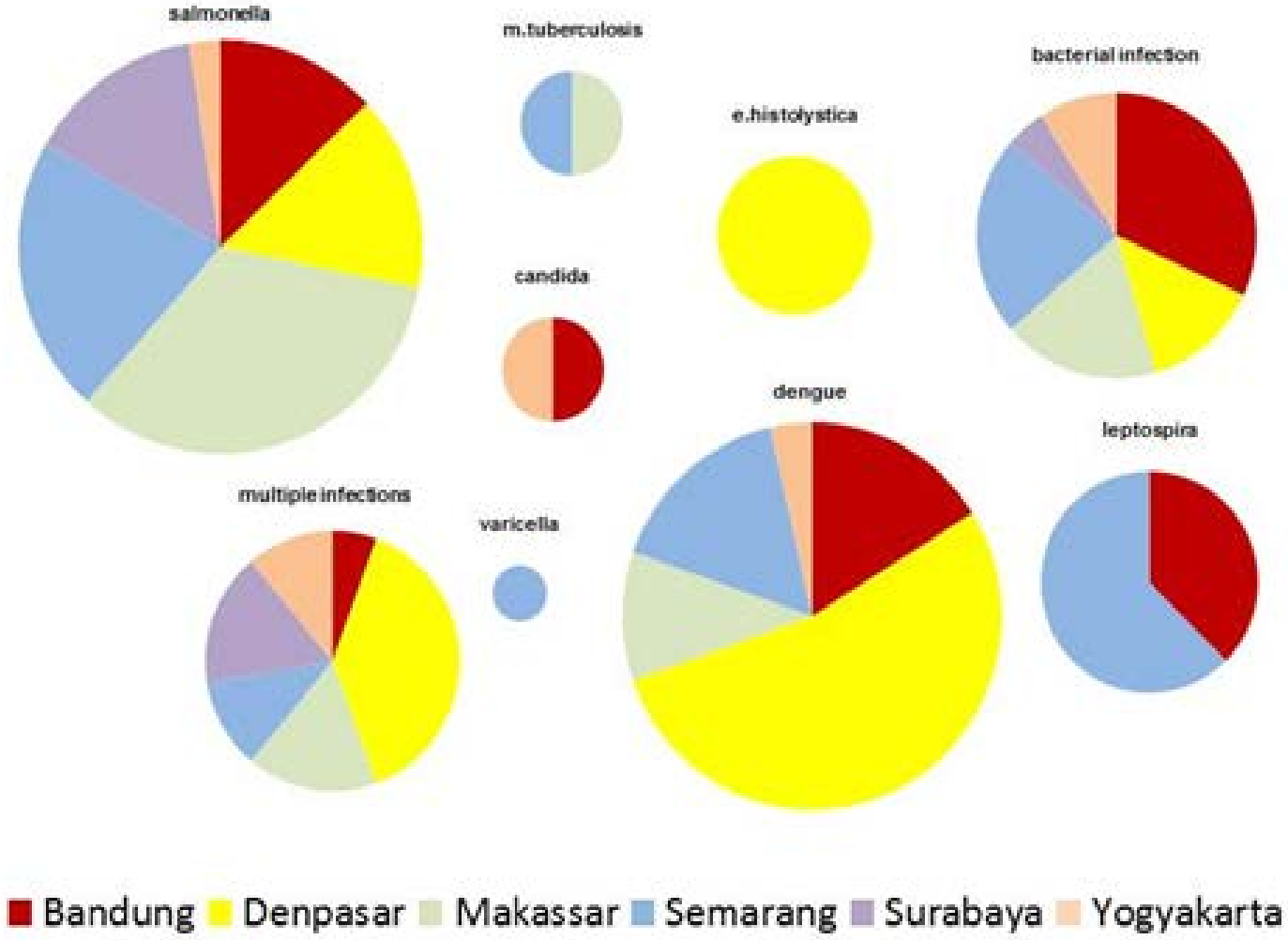
(5) E, coli

(2) Streptococcus viridans
(2) Acinetobacter baumannii
(2) Amoeba intestine
(2) Pneumonia: K. pneumonia
(2) SLE
(2) Ulkus diabetic pedis; Enterococcus faecalis

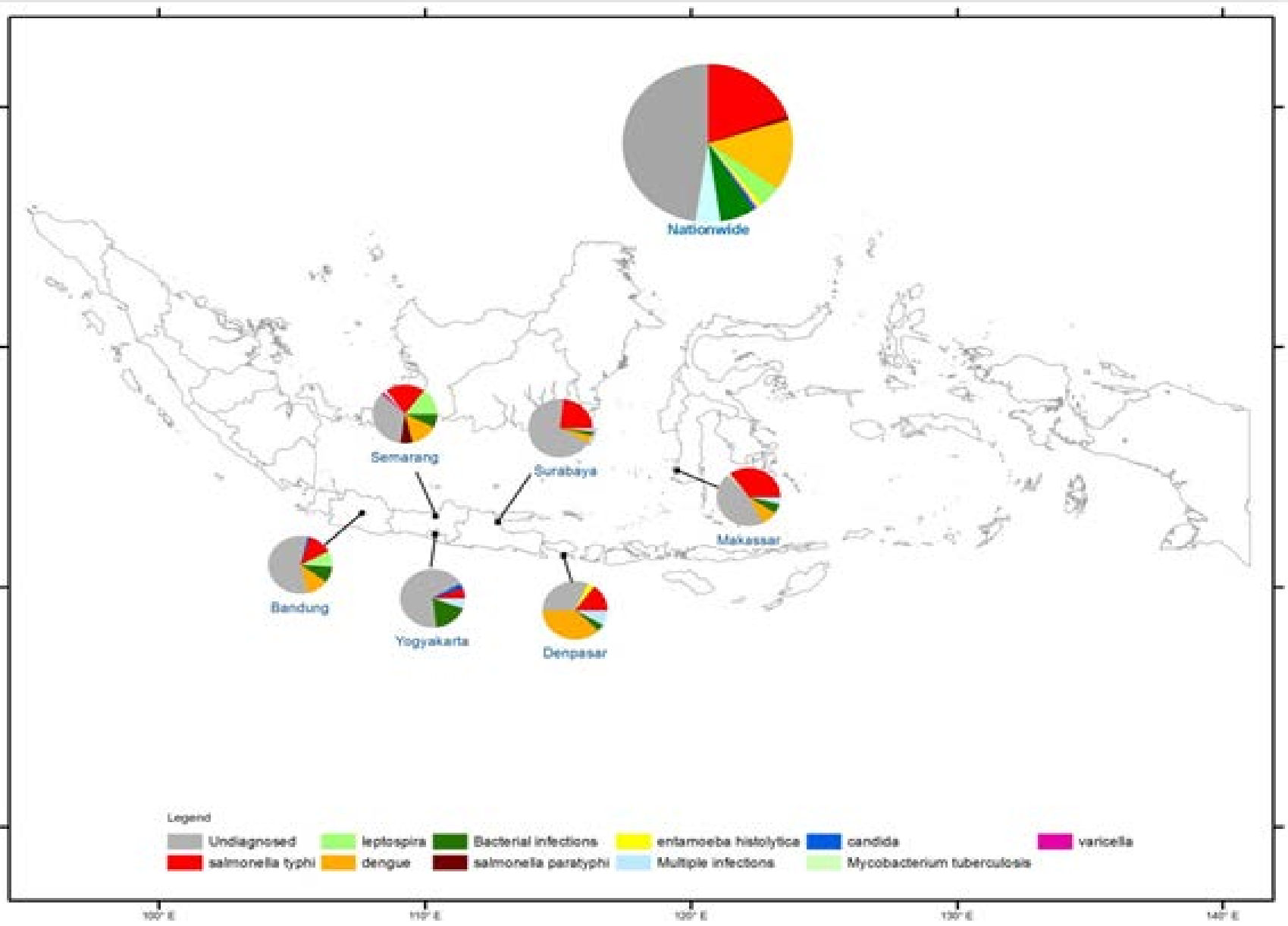
(4) HIV

(1) Pseudomonas aeruginosa
(1) Staphylococcus hominis
(1) Abses hepar piogenik: K. pneumonia
(1) Candida albicans
(1) Candida albicans, Candida non albicans, Pseudomonas cepacia, Pseudomonas aeroginosa
(1) Candida non albicans
(1) Dengue, GEA; EPEC
(1) Disentri Amoeba
(1) Enterobacter cloacae
(1) Hepatitis B, Enterobacter aerogenes, Streptococcus non hemolyticus
(1) Klebsiella pneumoniae
(1) M. tuberculosis, HIV
(1) M. tuberculosis, Streptococcus viridans, Candida albicans, Pantoea spp
(1) Mycobacterium leprae
(1) Pielonefritis: Micrococcus
(1) Pneumonia: Candida non candida albicans
(1) Pneumonia: Enterobacter aerogenes, Candida non albicans
(1) Pneumonia: Moraxella
(1) Proteus mirabilis, Streptococcus faecalis
(1) Pseudomonas sp.
(1) Pus ulkus pedis kaki kanan: Staphylococcus aureus, Streptococcus viridans, Pseudomonas aeruginosa
(1) Salmonella, CAP: Streptococcus
(1) Salmonella, E.histolitica
(1) Salmonella, M. tuberculosis
(1) Salmonella, M. tuberculosis, HIV
(1) Salmonella, UTI: E.coli
(1) Soft Tissue infection (Diabetic foot) : Proteus mirabilis
(1) Soft Tissue infection (Diabetic foot) :Staphylococcus aureus
(1) Staphylococcus hemoliticus
(1) Ulkus diabetik pedis dextra wagner IV: Enterococcus aerium
UTI: Enterococcus

Frequency distribution of etiologies



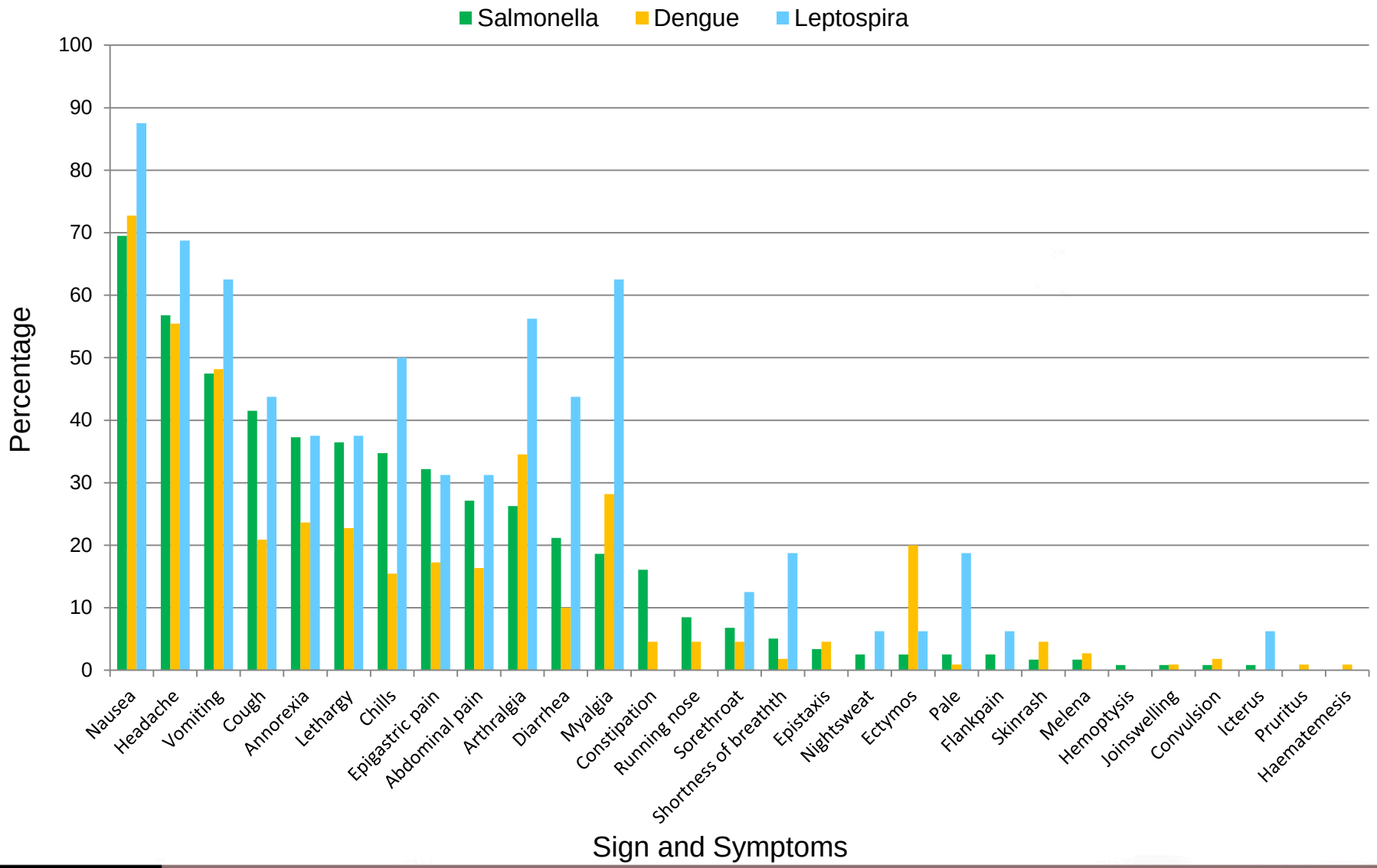
Distribution of etiologies in each hospital



Mixed Infections

Etiologies	number
Dengue + Salmonellae	10
Dengue + EPEC (feses)	1
Salmonellae + *E Coli* (urine)	1
Salmonellae + HIV + MTB	1
Salmonellae + MTB	1
Salmonellae + *Streptococcus sp* (sputum)	1
Salmonellae + *E histolytica*	1
Hepatitis B + *E aerogenes* (sputum)	1
MTB + HIV	1

Signs and Symptoms in Salmonellae, Dengue and Leptospira infections



Fatal Cases by Age Group and Site (n=37)

Age Group (y.o)	Site 510 (N=7)	Site 520 (N=7)	Site 550 (N=7)	Site 560 (N=2)	Site 570 (N=5)	Site 580 (N=9)	ALL
1-4	10% (2/20)	0% (0/5)	0% (0/9)	0% (0/14)	0% (0/13)	12.5% (3/24)	5.9% (5/85)
5-17	0% (0/43)	0% (0/35)	14.3% (2/14)	0% (0/30)	4.2% (1/24)	0% (0/18)	1.8% (3/164)
>17	6.3% (5/79)	8.6% (7/81)	6.8% (5/74)	2.9% (2/68)	8.2% (4/49)	17.1% (6/35)	7.5% (29/386)
All	**4.9% (7/143)**	**5.8% (7/121)**	**7.2% (7/97)**	**1.8% (2/112)**	**5.8% (5/86)**	**11.7% (9/77)**	**5.8% (37/636)**

Preliminary findings

- **In about half of pts with AFI, etiologies unknown**
- **Salmonellae, Dengue virus and Leptospira are major etiologies**

Near Future Plans

- **Identifying etiologies of unconfirmed or undiagnosed cases**
- **Further testing of all stored samples**
- **Other studies based on interesting (preliminary) findings**
- **Publications**

Identifying etiologies in unconfirmed/undiagnosed cases

- **16s RNA PCR**
- **Rickettsia**
- **Leptospira**
- **Viruses**


THANK YOU