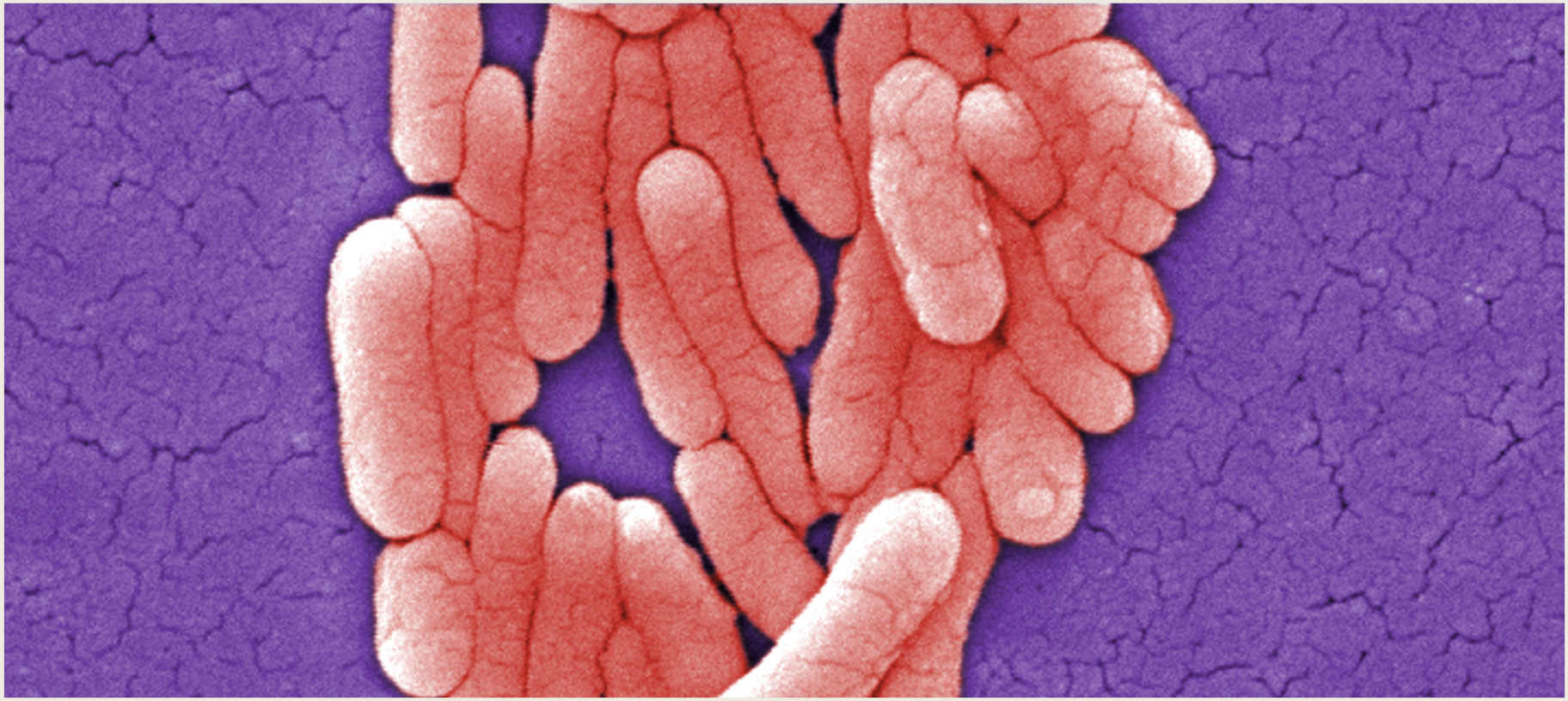


Addressing Confusion in Common Pediatric Infections:

Typhoid Fever

Gyneth Lourdes G. Bibera , MD, FPPS, FPIDSP

Disclosure of Interest

Medical Manager, GlaxoSmithKline

Asia Pacific Region

Agenda

- General Realities in Typhoid Fever
- Case Scenario: Addressing the Challenge in the Diagnosis and Management of Typhoid Fever
- Preventive measures

General Realities in Typhoid Fever

Remains to be a global health problem

- Annual incidence: 17M cases
  - 420,000 deaths occur annually in Asia
  - Case fatality rate without treatment : 10%

Common in 3-19 years old

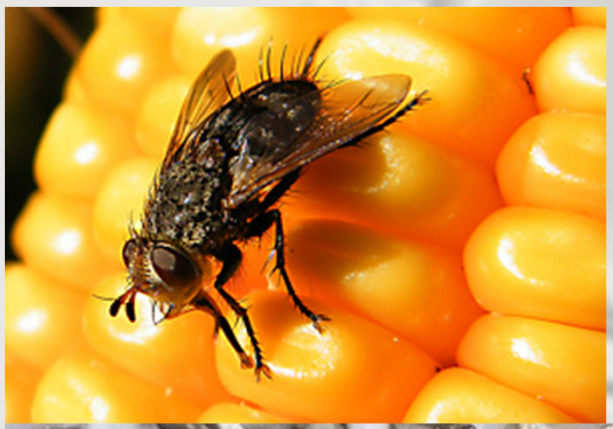
Humans are the only natural host and reservoir

2-5% become chronic carriers

S. typhi had become increasingly resistant to a number of 1st line antibiotics

WHO: Guidelines for Typhoid Fever 2011
Weekly EWARN Summary Focus on Typhoid Fever WHO Philippines January 2014

General Realities in Typhoid Fever



- Period of communicability
  - As long as infected person excretes *S. typhi* (after 1st week of illness up to convalescence)
- Mode of transmission:
  - Person to person via feco-oral route
    - Shellfish and vegetable grown in sewage contaminated water
    - Flies can mechanically transfer organism to food
    - Inoculum size influence attack rate and incubation period (Infecting dose, ID50, is 1,000,000 organism)

WHO: Guidelines for Typhoid Fever 2011

COMPARATIVE Statistics - Confirmed Typhoid Cases January to December 2013, Philippines

Occurs in all age group- peaks 5-14 years
Increasing incidence in the 1-4 age group

Category		Cases	% of Total	5-Year Median	% Change from 5-Year Median	Deaths	CFR (%)
Sex	Male	438	50.11%	282	55.32%	1	0.23%
	Female	436	49.89%	233	87.12%	1	0.23%
Age group (Years)	<1	13	1.49%	12	8.33%	0	0.00%
	1 to 4	169	19.34%	66	156.06%	0	0.00%
	5 to 14	325	37.19%	183	77.60%	0	0.00%
	15 to 24	154	17.62%	107	43.93%	0	0.00%
	25 to 39	110	12.59%	80	37.50%	1	0.91%
	40 to 64	84	9.61%	64	31.25%	1	1.19%
	65 & up	19	2.17%	15	26.67%	0	0.00%

PIDSR 2013

Typhoid in younger children

Recent data from South Asia indicate that the presentation of typhoid may be more dramatic in children younger than 5 years, with higher rates of complications and hospitalization.

Diarrhea, toxicity, and complications such as disseminated intravascular coagulation are also more common in infancy, with higher mortality.

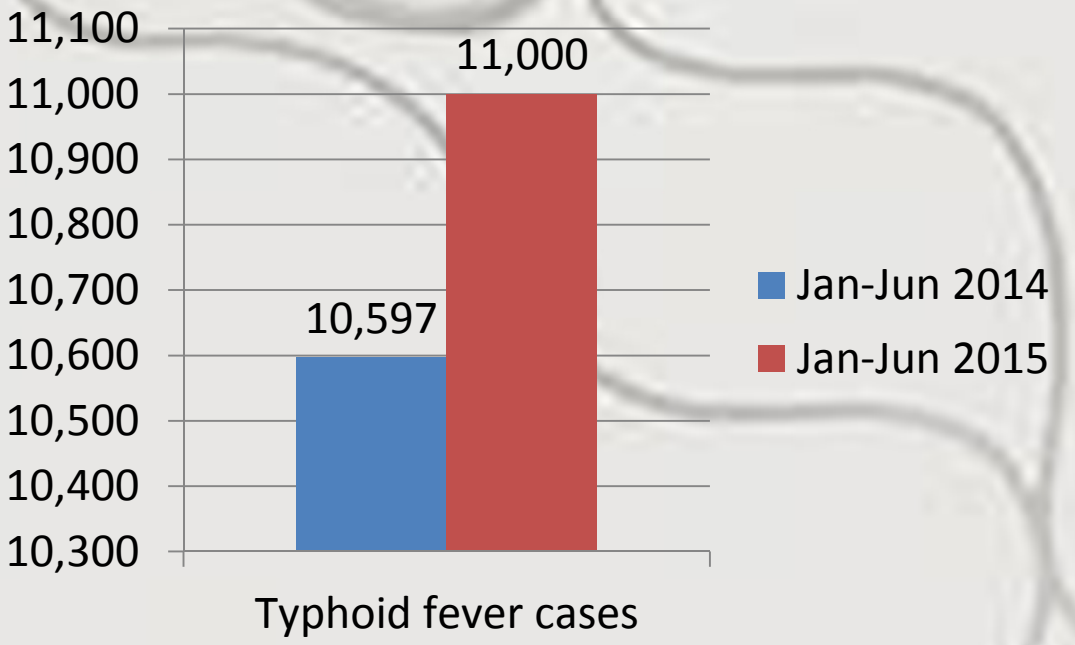
COMPARATIVE Statistics Confirmed Typhoid Cases January to December 2013, Philippines

Category		Cases	% of Total	5-Year Median	% Change from 5-Year Median	Deaths	CFR (%)
Region	I	30	3.43%	5	500.00%	0	0.00%
	II	470	53.78%	109	331.19%	0	0.00%
	III	39	4.46%	6	550.00%	0	0.00%
	IVA	66	7.55%	113	-41.59%	1	1.52%
	IVB	28	3.20%	41	-31.71%	0	0.00%
	V	6	0.69%	12	-50.00%	0	0.00%
	VI	6	0.69%	9	-33.33%	0	0.00%
	VII	20	2.29%	65	-69.23%	0	0.00%
	VIII	8	0.92%	8	0.00%	0	0.00%
	IX	10	1.14%	17	-41.18%	0	0.00%
	X	4	0.46%	31	-87.10%	0	0.00%
	XI	2	0.23%	0	0.00%	0	0.00%
	XII	64	7.32%	11	481.82%	0	0.00%
	ARMM	49	5.61%	4	1125.00%	0	0.00%
	CAR	9	1.03%	1	800.00%	0	0.00%
	CARAGA	45	5.15%	41	9.76%	1	2.22%
	NCR	18	2.06%	61	-70.49%	0	0.00%

PIDSR 2013

Typhoid fever is here to stay!

- Cases of typhoid fever slightly increased in 2015.
  - 11 people have died from typhoid. Region X, or Northern Mindanao reported 2,656 cases accounting for nearly a quarter of all cases.



Philippines Reportable Diseases update for 2015
August 8, 2015

Philippines **Continue** to report OUTBREAKS


CEBU DAILY NEWS NEWS OPINION COMMUNITY WHAT'S UP SILOY IS WATCHING MULTIMEDIA PHOTO STORE

DOH verifying reports of typhoid fever epidemic

March 2015

Michelle Joy L. Padayhag | 9:47 AM | Tuesday, March 3rd, 2015

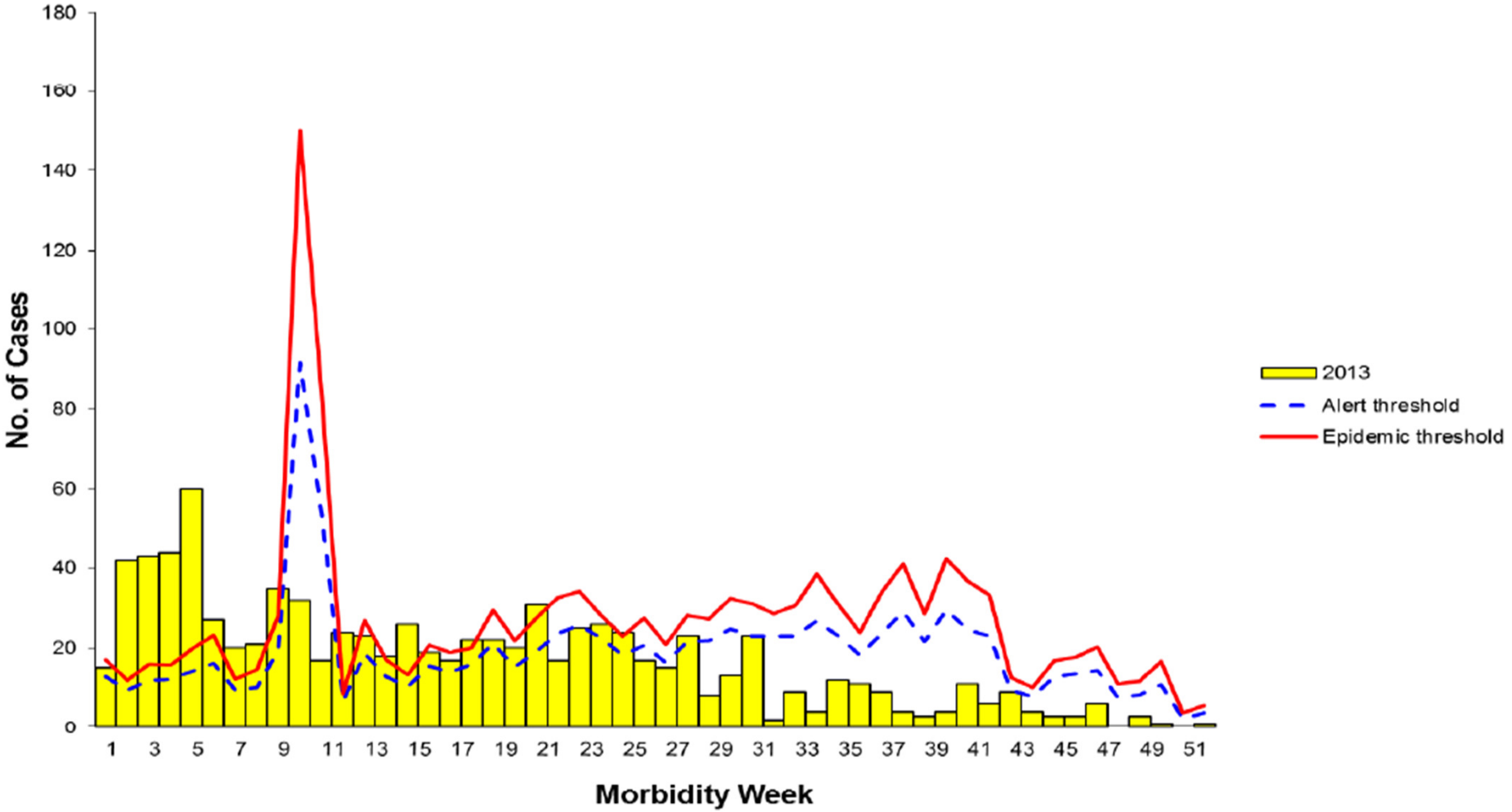
@cebudailynews

Typhoid outbreak in Borongan City now under control, DOH-8 says August 2015

Typhoid outbreak hits more than 1,400 in Philippines - CALAMBA 2008

A typhoid fever outbreak was declared in four sitios in Barangay Datal Anggas in Alabel, Sarangani as early as February 2010

Distribution of Confirmed Typhoid Cases by Morbidity Week



PIDSR 2013

Standard Case Definition of Typhoid

Confirmed Case	**• A patient with persistent fever (38°C) lasting for 3 or more days with laboratory confirmed *S. typhi* organisms (blood bone marrow, bowel fluid) •A clinical compatible case that is laboratory confirmed**
Probable Case	•A patient with persistent fever (38°C) lasting for 3 or more days , with a positive serodiagnosis or antigen detection test but no *S. typhi* isolation •A clinical compatible case that is epidemiologically linked to a confirmed case or outbreak
Chronic carrier	An individual excreting *S. typhi* in the stool or urine for longer than one year after the onset of typhoid fever

WHO: Guidelines for Typhoid Fever 2011

General Realities in Typhoid Fever

WIDE SPECTRUM

Mild illness with low grade fever, malaise and dry cough

Severe clinical picture- abdominal discomfort, altered mental status, multiple complications

Non –epidemic occurrences

Outbreaks

WHO: Guidelines for Typhoid Fever 2011

General Realities in Typhoid Fever

Difficult to ESTIMATE real burden

- Clinical picture non-specific
- UNDER-estimated
  (or over-estimated?)

WHO: Guidelines for Typhoid Fever 2011

General Realities in Typhoid Fever

- Difficulties:
  - Diagnosis in the 1st week of illness: symptoms are of generalized infections without localizing features
  - Antibiotic therapy complicates course of illness and isolation of etiologic agent
  - Mostly relies on serologic tests (cultures are slower) - interpretation dependent

Diagnosis is a challenge

Case scenario

- History:

10 year old boy, studies in a public elementary school in QC.

fever x 5days; slight headache; vague abdominal pain; with one episode of vomiting ; mild dry cough with nose stuffiness; decrease in appetite

No history of travel

- PE: temp =38.9^{o}C, HR=90/min, RR=20/min; BP= 90/60
  - dry-looking, with poor disposition; weak-looking; clear breath sounds; no abdominal tenderness; slightly enlarged liver

First Impression?

DENGUE?

INFLUENZA?

TYPHOID?

The often non-specific symptoms of typhoid fever can make its clinical diagnosis difficult and it can be confused with malaria, dengue fever, influenza and other febrile illnesses

Establishing Useful Clues in Diagnosis

Ask about the following to determine possible source of infection:

- Persons with similar symptoms (household members, sexual partners, day care children)
- Food history: consumed at home, restaurants, parties, during travel
- Water source?
- Identify state of hygiene/sanitation
- Exposure history : possible exposure to a typhoid carrier
- Travel history

WHO: Guidelines for Typhoid Fever 2011

Common Clinical Features of Typhoid Fever in children

Features	Rate (%)
High grade fever	95
Coated tongue	76
Anorexia	70
Vomiting	39
Hepatomegaly	37
Diarrhea	36
Toxicity	29
Abdominal pain	21
Pallor	20
Splenomegaly	17
Constipation	7
Headache	4
Jaundice	2
Obtundation	2
Ileus	1
Intestinal perforation	0.5

Coated tongue

Can Typhoid be diagnosed CLINICALLY WHEN it matters?

Nelson's Textbook of Pedtrics 20th edition
Bhutta et al. BMJ VOLUME 333 8 JULY 2006

The challenge of NON-SPECIFIC signs and symptoms- TIMING is key!

Signs and Symptoms	Week 1	Week 2	Week 3
Systemic			
High grade fever			
Anorexia	Almost all		
Chills	Almost all		
Neurologic			
Malaise	Almost All		
Insomnia			Typhoid state
Confusion/delirium	Common		
Psychosis			
Headache(frontal)			
Ear, nose throat			
Coated tongue			

= common =very common/almost all

WHO: Guidelines for Typhoid Fever 2011

The challenge of NON-SPECIFIC signs and symptoms- TIMING is key!

Signs and Symptoms	Week 1	Week 2	Week 3
Pulmonary			
Mild cough			
Gastrointestinal			
Constipation			
Diarrhea			
Bloating			
Diffuse abdominal pain			
GI hemorrhage			
Intestinal perforation			Rare
Heptosplenomegaly			
Cardiovascular			
dicrotic pulse			

= common =very common/almost all

WHO: Guidelines for Typhoid Fever 2011

Other Useful Clues in Diagnosis

Temperature Pattern:

- rises in small increments
- Usually reaches 40-40.5^{o}C by the end of the 1st week
- Does not return to normal; rises to peak every afternoon
- Unremitting

- Constipation : in older Children
- Diarrhea : follows fever (greenish pea soup)- 2nd week
- Relative bradycardia: over the 1st week but not constant finding

Duration of fever was the only significant predictor for typhoid fever.

Feigin and Cherry . Textbook of Infectious Diseases
Thriemer, K. Plos One December 2013

Other Useful Clues in Diagnosis

" TOXIC facies, coated tongue,
MUSTY, DAMP-like Odor,
Tender doughy abdomen,
occasional low level cough"

Persistence of fever usually more than 7 days
with bowel changes plus neurologic manifestations

Feigin and Cherry . Textbook of Infectious Diseases

Case Scenario

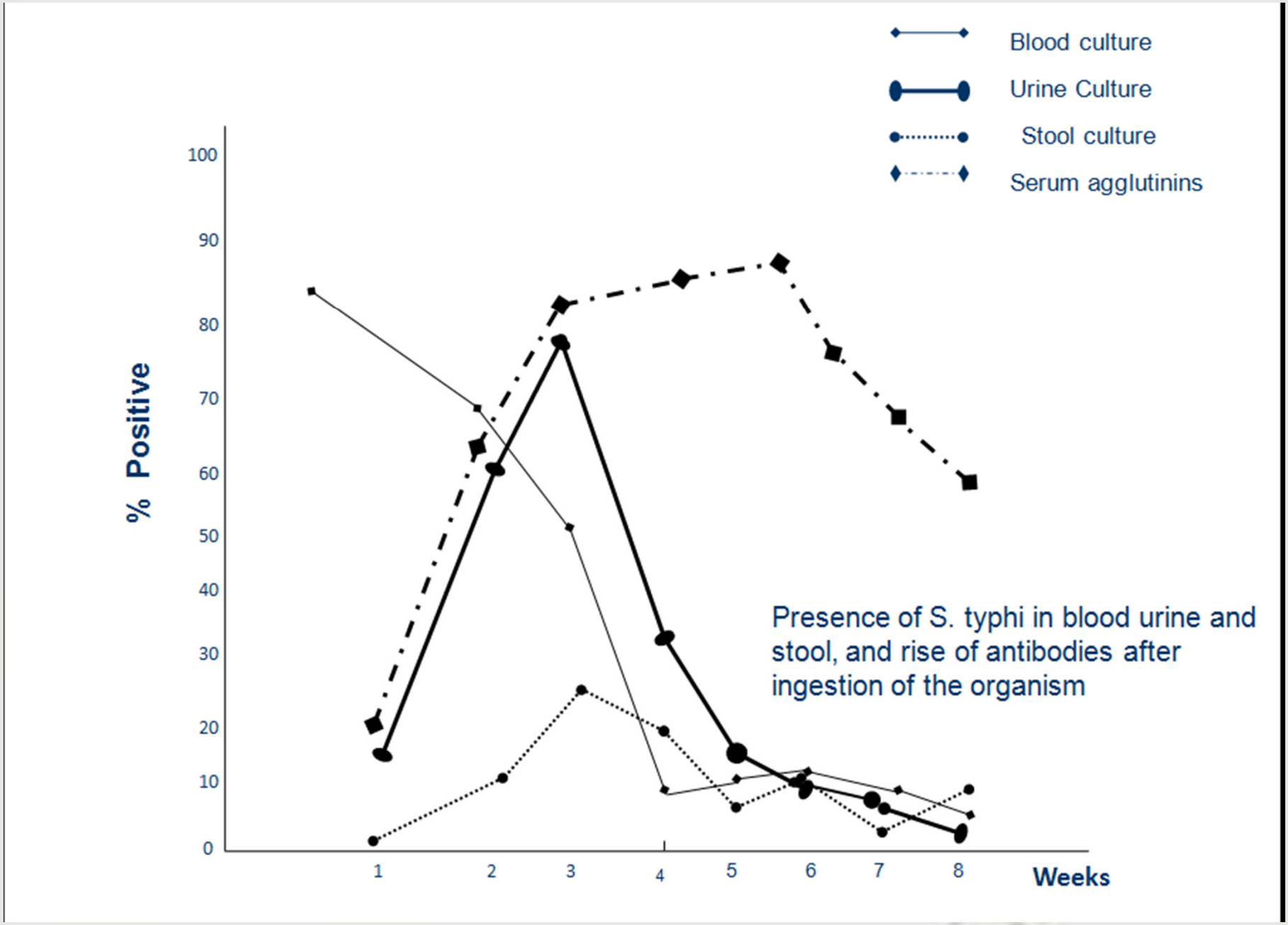
- Laboratory Tests:
  - CBC: Hgb: 12; Hct 38 WBC: 8 Segmenters : 60% lymphocytes 40% ; platelet count 150 T
  - Urinalysis: normal
  - Chest Xray : normal
  - Typhidot : positive
  - Blood culture done

The challenge of APPRORIATE diagnostics in typhoid

Culture:

- blood culture, positive in only 40-60% of cases, usually early in the course of the disease.
  - 10-15 ml : school children and adults
  - 2-4 ml: toddlers and pre-school children
- Stool and urine cultures become positive after the first week of infection, but their sensitivity is much lower
  - Stool CS: useful dx test for chronic carriers
- Bone Marrow: more sensitive but invasive

Bhutta et al. BMJ VOLUME 333 8 JULY 2006
WHO: Guidelines for Typhoid Fever 2011


Blood culture
Urine Culture
Stool culture
Serum agglutinins
% Positive
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6
7
8
Weeks
Presence of S. typhi in blood urine and stool, and rise of antibodies after ingestion of the organism

The challenge of APPRORIATE diagnostics in typhoid

WIDAL TEST

- Serologic assay →detecting antibodies to the O and H antigens
  - becomes positive in 7-10 days
    - A four-fold rise in titer
  - A single titer of >1/160 WITH compatible clinical illness
  - False positive/negative results are common

Bhutta et al. BMJ VOLUME 333 8 JULY 2006
WHO: Guidelines for Typhoid Fever 2011

The challenge of APPRORIATE diagnostics in typhoid: Rapid antibody tests

Test Kit	Sensitivity(%)	Specificity(%)	PPV%	NPV%
TUBEX® Africa Philippines	 73.0 (60.3–83.4) 94.7 (86.2–98.3)	 69.0 (49.2–84.7 80.4 (71.1–87.3)	 54.0 78.0	 83.6 95.3
Typhidot® IgM Africa Philippines	 75.0 (61.1–86.0) 54.7 (42.8–66.1)	 60.7 (40.6–78.5) 64.7 (54.6–73.7)	 56.7 53.0	 78 66.0
Typhidot® IgG Africa Philippines	 69.2 (54.9–81.3) 73.3 (61.7–82.6)	 70.4 (49.8–86.2) 46.1 (36.3–56.2)	 54.3 50.0	 81.8 70.1

Bulletin of the WHO Volume 89, Number 9, September 2011, 640-647
Kawano et al JOURNAL OF CLINICAL MICROBIOLOGY, Jan. 2007, p. 246–247

The challenge of APPRORIATE diagnostics in typhoid

Other hematological investigations are NON-SPECIFIC.

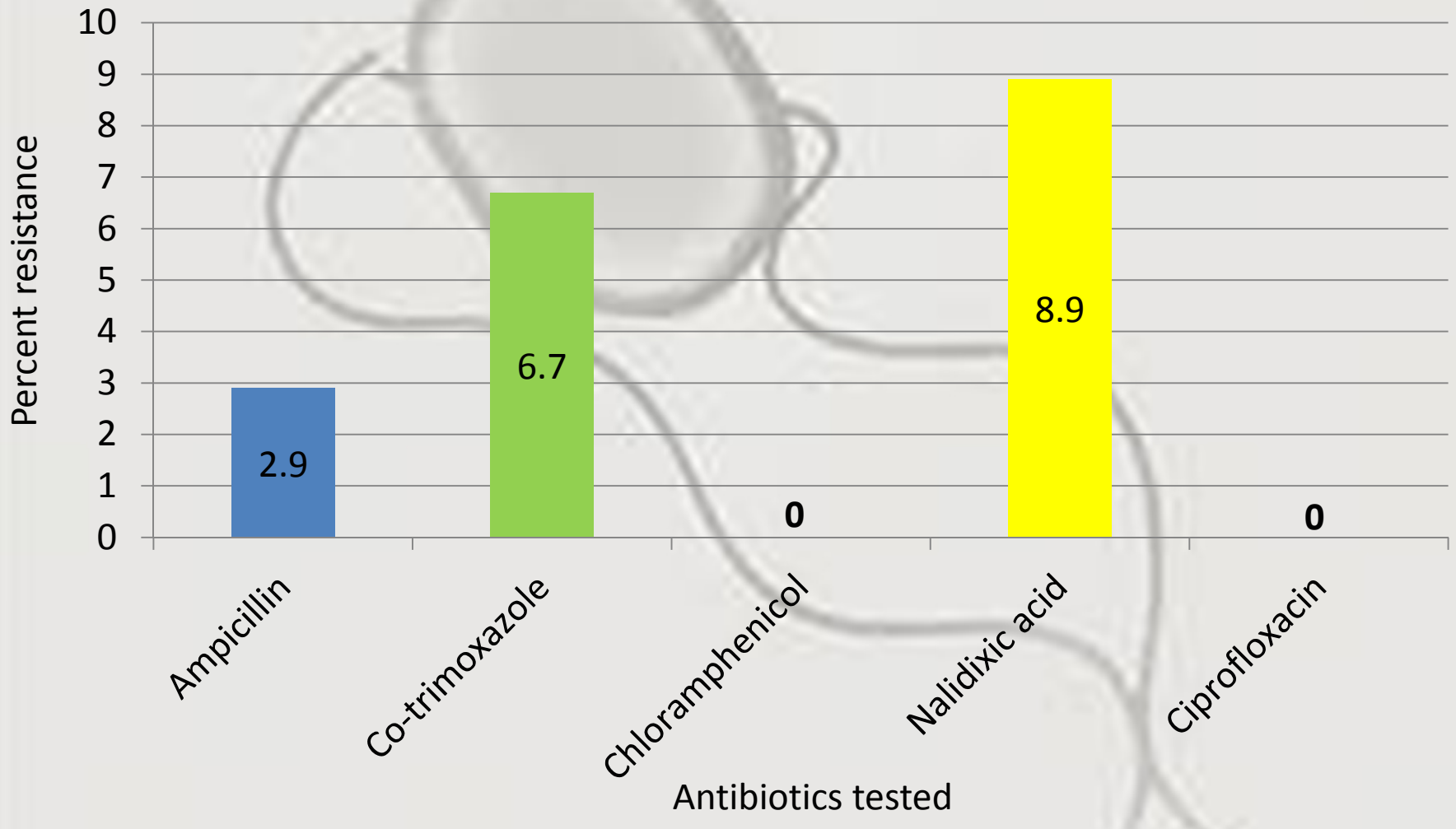
- Blood leucocyte counts are often low in relation to the fever and toxicity, but the range is wide; in younger children leucocytosis is a common association and may reach 20 000-25 000/mm3.12 w4
- Thrombocytopenia may be a marker of severe illness and accompany disseminated intravascular coagulation.
- Liver function test results may be deranged, but significant hepatic dysfunction is rare.

Case scenario

- Fever persists with occurrence of 3-4 episodes of loose stools per day. Patient is irritable;
- What is your antibiotic management?

A. Chloramphenicol
B. Ceftriaxone
C. Cefixime
D. Ciprofloxacin

Percent Resistance of *Salmonella Typhi, ARSP, 2014*



Carlos, C. ARSP 2014

WHO Management Guideline

Susceptibility	Optimal treatment: Drug	Optimal treatment: Daily dose (mg/kg)	Optimal treatment: Course (days)	Alternative effective treatment: Drug	Alternative effective treatment: Daily dose (mg/kg)	Alternative effective treatment: Course (days)
Uncomplicated typhoid fever						
Fully sensitive	Fluoroquinolone (such as ofloxacin or ciprofloxacin)	15	5-7*	Chloramphenicol	50-75	14-21
				Amoxicillin	75-100	14
				TMP-SMX	8-40	14
Multidrug resistance	Fluoroquinolone *or*	15	5-7	Azithromycin	8-10	7
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone resistance†	Azithromycin *or*	8-10	7	Cefixime	20	7-14
	Ceftriaxone	75	10-14			
Severe typhoid fever requiring parenteral treatment						
Fully sensitive	Fluoroquinolone (such as ofloxacin)	15	10-14	Chloramphenicol	100	14-21
				Ampicillin	100	14
				TMP-SMX	8/40	14
Multidrug resistant	Fluoroquinolone	15	10-14	Ceftriaxone *or*	60	10-14
				Cefotaxime	80	
Quinolone resistant	Ceftriaxone *or*	60	10-14	Fluoroquinolone	20	14
	Cefotaxime	80				

*Three day courses also effective, particularly so in epidemic containment.
†Optimum treatment for quinolone resistant typhoid fever has not been determined. Azithromycin, third generation cephalosporins, or a 10-14 day course of high dose fluoroquinolone is effective. Combinations of these are now being evaluated.

Recommended Antibiotic Treatment for Typhoid Fever

Susceptibility	Antibiotic	Daily dose (mg/kg)	Days
Fully susceptible	Chloramphenicol *or* Amoxicillin *or* Trimethoprin sulfamethoxazole *or* 3rd generation cephalosporin (eg cefixime) *or* Flouroquinolone (eg. Ofloxacin or ciprofloxacin)	50-75 75-100 8/40 15-20 30	14-21 14 14 7-10 7-10
Multi-drug resistant	Azithromycin 3rd generation cephalosporin (eg cefixime) *or* Flouroquinolone (eg. Ofloxacin or ciprofloxacin)	20 15-20 30	5-7 7-10 7-10
Quinolone resistant	Azithromycin 3rd generation cephalosporin (eg cefixime) *or* Parenteral 3rd generation cephalosporin (eg ceftriaxone Flouroquinolone (eg. Ofloxacin or ciprofloxacin)	20 20 80 30	5-7 7-10 7-10 7-10

Feigin and Cherry . Textbook of Infectious Diseases

Management of Typhoid Fever

- Antibiotic response
  - Slow (fever may persist for many days een after bacteremia has resolved)
  - Ciprofloxacin defervescence: 3.3 to 4.2 days; lower relapses

Feigin and Cherry . Textbook of Infectious Diseases

Prevention through Immunization

"The importance of vaccination and other preventive measures for typhoid fever is heightened by increasing resistance of *Salmonella serotype Typhi to antimicrobial agents, including fluoroquinolones, in many parts of the world"*

Updated Recommendations for the Use of Typhoid Vaccine — Advisory Committee on Immunization Practices, United States, 2015 MMWR March 2015

Prevention through Immunization

- Two typhoid vaccines are currently recommended for use:
  - an injectable polysaccharide vaccine based on the purified Vi antigen (known as Vi-PS vaccine) **for persons aged two years and above**
  - a live attenuated oral Ty21a vaccine in capsule formulation **for those over five years of age**

Weekly epidemiologocal report 8 FEBRUARY 2008, 83rd YEAR / 8 FÉVRIER 2008, 83e ANNÉE
No. 6, 2008, 83, 49–60 http://www.who.int/wer8

Prevention through Immunization WHO Recommendation

Countries should consider the programmatic use of typhoid vaccines for controlling endemic disease.

- Most countries, control will require vaccination only of high-risk groups and populations

Given the epidemic potential ,vaccination recommended for outbreak control.

Weekly epidemiologocal report 8 FEBRUARY 2008, 83rd YEAR / 8 FÉVRIER 2008, 83e ANNÉE
No. 6, 2008, 83, 49–60 http://www.who.int/wer8

Prevention through Immunization WHO Recommendation

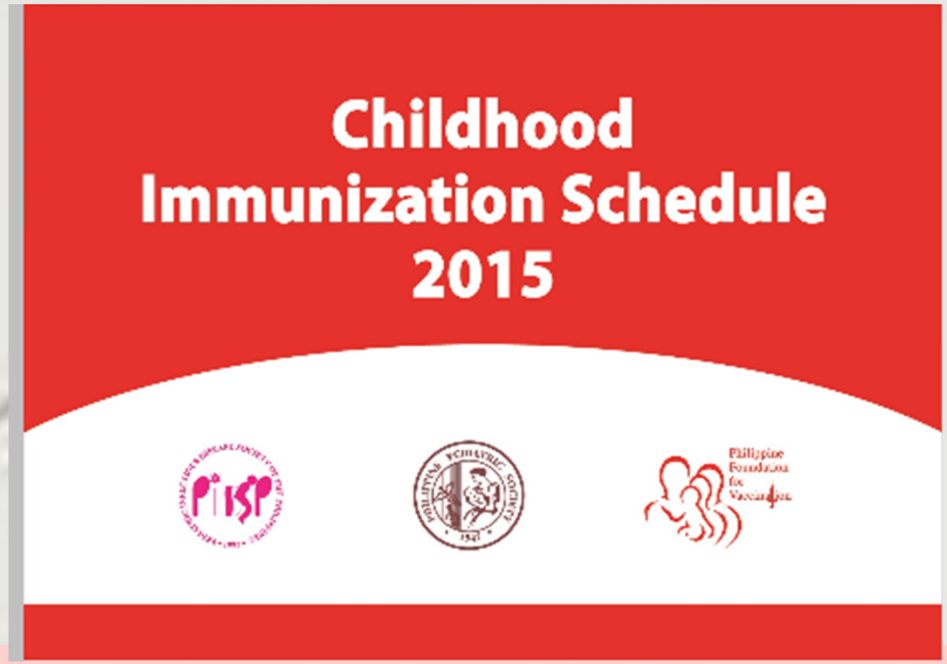
School-age and/or preschool-age children : significant public health problem in this groups, where antibiotic-resistance is prevalent.

Travellers especially to those staying in endemic areas for >1 month and/or in locations where antibiotic resistant strains of S. Typhi are prevalent.

All typhoid fever vaccination programmes should be implemented in the context of :

- other efforts to control the disease (health education, water quality and sanitation improvements, and training of health professionals in diagnosis and treatment.)

Weekly epidemiologocal report 8 FEBRUARY 2008, 83rd YEAR / 8 FÉVRIER 2008, 83e ANNÉE
No. 6, 2008, 83, 49–60 http://www.who.int/wer8



VACCINES FOR SPECIAL GROUPS

TYPHOID VACCINE

Given IM

Given at a minimum age of 2 years old with revaccination every 2-3 years

Recommended for travellers to areas where there is a risk of exposure and for Outbreak situations as declared by public health authorities

PIDSP, PPS, PFV Childhood Immunization schedule 2015

Important Health Messages

- Practice hand washing with soap and running water before food preparation and eating
- Eat foods that have been thouroghly cooked and that are hot and steaming
- Ensure that cooked food is covered to protect it from flies
- Avoid raw vegetables and fruits that cannot be peeled
- Peel fruits and vegetables yourself
- Avoid food and beverages from street vendors
- Boil all drinking water at least 1 minute
- Ask for drinks without ice
- Avoid flavored ice and juice
- Properly refrigerate food where possible

WHO: Guidelines for Typhoid Fever 2011

Summary

Typhoid remains to be a public health concern especially in developing countries like the Philippines

Because of then-specificity of initial signs and symptoms (and lab exams), diagnosis may be difficult at the onset of disease

Prevention through immunization is largely dependent on the epidemiology of the disease

Summary

ENJOY THE REST OF THE CONFERENCE!