# Infectious Bloody Diarrhea in Children

MA. LIZA ANTOINETTE M. GONZALES, MD, FPPS, FPIDSP

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# Bloody Diarrhea

- Any diarrheal episode in which loose or watery stools contain red visible blood
- Usually a sign of invasive enteric infection with pathogens that invade the bowel mucosa
- Indicates inflammation and tissue damage

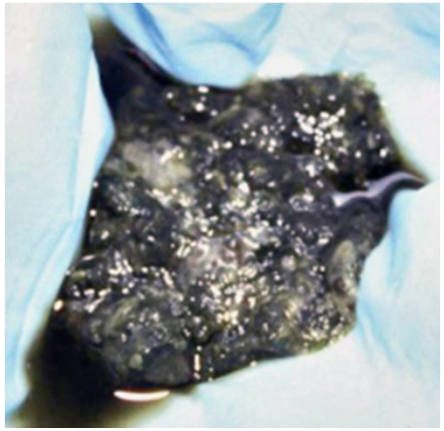
WHO. The Management of Bloody Diarrhoea in Young Children. WHO/CDD/94.49

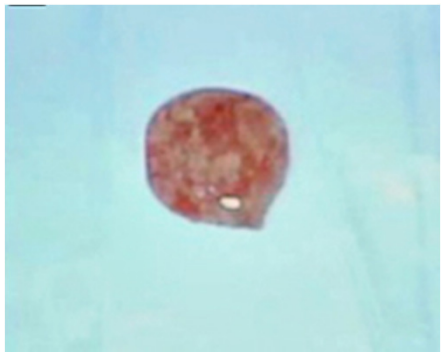
# Gastrointestinal Bleeding

- **Melena** - describes stools that appear black and tar-like, usually suggests UGIB; certain medications (e.g.iron) or food (large amounts of dark green leafy vegeables) may present as black stool but *do not contain blood*.

- **Hematochezia** - passage of bright red blood per rectum, usually suggests LGIB from the colon or anus; mucoid or watery stool with blood

- **Occult GI bleeding** - not visible to the patient or physician; usually presents as iron deficiency anemia or identified by testing for stool occult blood



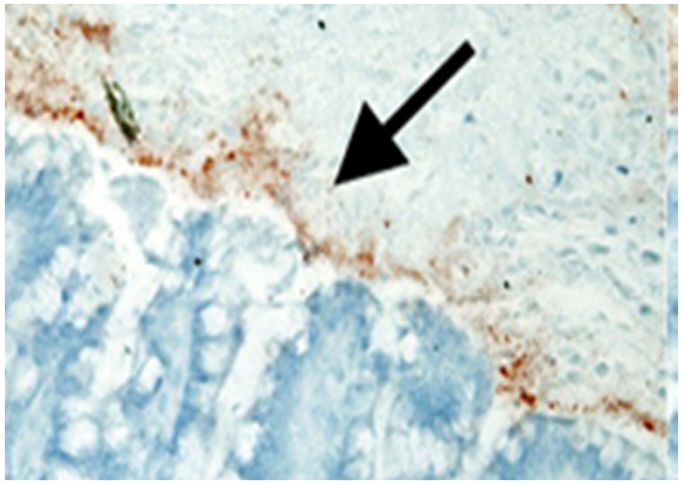




WHO. The Management of Bloody Diarrhoea in Young Children. WHO/CDD/94.49

# Acute Dysentery

- Syndrome of bloody diarrhea with fever, abdominal cramps, tenesmus or painful defecation
- Implies inflammatory colitis or invasion and destruction of colonic mucosa by bacteria, cytotoxic products or parasites
- Pathologic changes:



superficial colonic lesions

deep colonic lesions

WHO. The Management of Bloody Diarrhoea in Young Children. WHO/CDD/94.49

# Causes of Bloody Diarrhea in Infants and Children

| Infants aged ≤1 year | | Children aged >1 year | |
|---|---|---|---|
| **COMMON CAUSES** | **LESS COMMON / RARE CAUSES** | **COMMON CAUSES** | **LESS COMMON / RARE CAUSES** |
| **Intestinal infection**<br><br>**Infant colitis:**<br>• Non-specific colitis<br>• Breast milk colitis<br>• Cow's milk colitis | **Intestinal ischaemia**<br>• Intussusception<br>• Malrotation and volvulus<br>**Necrotising enterocolitis**<br>**Hirschsprung's disease**<br>**IBD**<br>• Crohn's colitis<br>• Ulcerative colitis<br>**Systemic vasculitis**<br>**Factitious illness** | **Intestinal infection**<br><br>**IBD**<br>• Crohn's colitis<br>• Ulcerative colitis<br><br>**Juvenile polyp** | **Intestinal ischaemia**<br>• Intussusception<br>• Malrotation and volvulus<br>**Mucosal prolapse syndrome**<br>**HSP or other forms of systemic Vasculitis**<br>**Factitious illness** |

Murphy MS. BMJ 2008;336:1010-5

# Epidemiology of Bloody Diarrhea in Children

- **Developed countries: bloody diarrhea in children is 15-20 times more likely to be caused by intestinal infection than IBD[1]**
  - UK: 50-75 per 100,000 of children will develop bloody diarrhea due to infectious causes (*Campylobacter, Salmonella, Yersinia*)
  - 2-3 per 100,000 of children present with bloody diarrhea as a result of IBD
- **Developing countries: *Shigella, Entamoeba histolytica* more likely cause of bloody diarrhea; Incidence of IBD is unknown[1]**
- **Bloody diarrhea is seen in 10% of diarrheal episodes in children < 5 years old; accounts for 15% of diarrhea-associated deaths worldwide[2]**
- **Compared with watery diarrhea, bloody diarrhea is more frequently associated with intestinal damage, nutritional deterioration, secondary sepsis, persistent diarrhea [3]**

1. Murphy MS. BMJ 2008;336:1010-5; 2.. WHO/CDD/94.49; 3. Keusch et al. Diarrheal Diseases In Disease Control Priorities in Developing Countries 2006

# Global Causes of Diarrheal Disease Mortality in Children <5 Years of Age: A Systematic Review

Claudio F. Lanata[1,2,3*], Christa L. Fischer-Walker[4], Ana C. Olascoaga[1], Carla X. Torres[1], Martin J. Aryee[5], Robert E. Black[4] for the Child Health Epidemiology Reference Group of the World Health Organization and UNICEF

| Pathogen | | Median (%) | No. of Deaths (x 1000) | 95% CI (x 1000) |
|---|---|---|---|---|
| VIRUSES | Rotavirus | 27.8% | 197 | 110-295 |
| | Calicivirus | 9.9% | 71 | 39-113 |
| | Adenovirus | 3.1% | 22 | 12-37 |
| BACTERIA | *EPEC* | 11.1% | 79 | 31-146 |
| | *ETEC* | 6.0% | 42 | 20-76 |
| | *Shigella sp.* | 3.9% | 28 | 12-53 |
| | *Campylobacter spp* | 3.2% | 22 | 11-50 |
| | *Salmonella spp.* | 2.5% | 18 | 10-30 |
| | *Vibrio cholerae 01* | 1.3% | 9 | 0-37 |
| PARASITES | Cryptosporidium | 2.0% | 14 | 3-31 |
| | *Giardia lamblia* | 2.3% | 16 | 0-66 |
| | *E. histolytica* | 0.2% | 1 | 0-19 |

# Acute Bloody Diarrhea in the Philippines, 2013

| Age Group (yrs) | Cases | Deaths (CFR%) |
|---|---|---|
| < 1 | 1729 | 11 (0.64%) |
| 1- 4 | 3262 | 8 (0.25%) |
| 5-14 | 1509 | 4 (0.27%) |
| 15-24 | 1304 | 2 (0.15%) |
| 25-39 | 1668 | 3 (0.18%) |
| 40-64 | 1825 | 4 (0.22%) |
| ≥65 | 761 | 2 (0.26%) |
| TOTAL | 12,058 | 34 (0.28%) |

PIDSR Annual Report 2013. DOH-NEC

# Infectious Causes of Acute Dysentery & Inflammatory Enterocolitis

## Specific Infectious Processes

- Bacillary dysentery: *Shigella spp.*; invasive *E. coli*
- *Salmonella spp*: nontyphoidal salmonella; *S. typhi*
- *Campylobacter jejuni*
- *Yersinia enterocolitica*
- *Entamoeba histolytica*
- *Vibrio parahaemolyticus*
- *Balantidium coli*
- *Trichinella spiralis*
- *Spirillum spp.*

## Proctitis

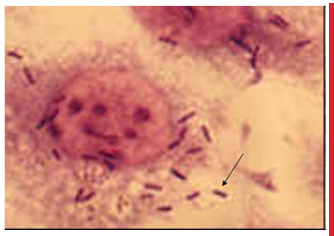
- *Neisseria gonorrhea*
- *Herpes simplex*
- *Chlamydia trachomatis*
- *Treponema pallidum*

## Other Syndromes

- Necrotizing enterocolitis
- Enteritis necroticans
- Pseudomembranous enterocolitis (*Clostridium difficile*)
- Typhlitis

Guerrant R & Lima A. Inflammatory Enteritides.In:Mandell, Douglas& Bennett's Principles and Practice of Infectious Diseases 5th ed.2000:1126-36; Arvola et al. Rectal bleeding in infancy.Pediatrics 2006;117:760-8; Murphy MS. Management of bloody diarrhoea in children in primary care. BMJ 2008;336;1010-15.

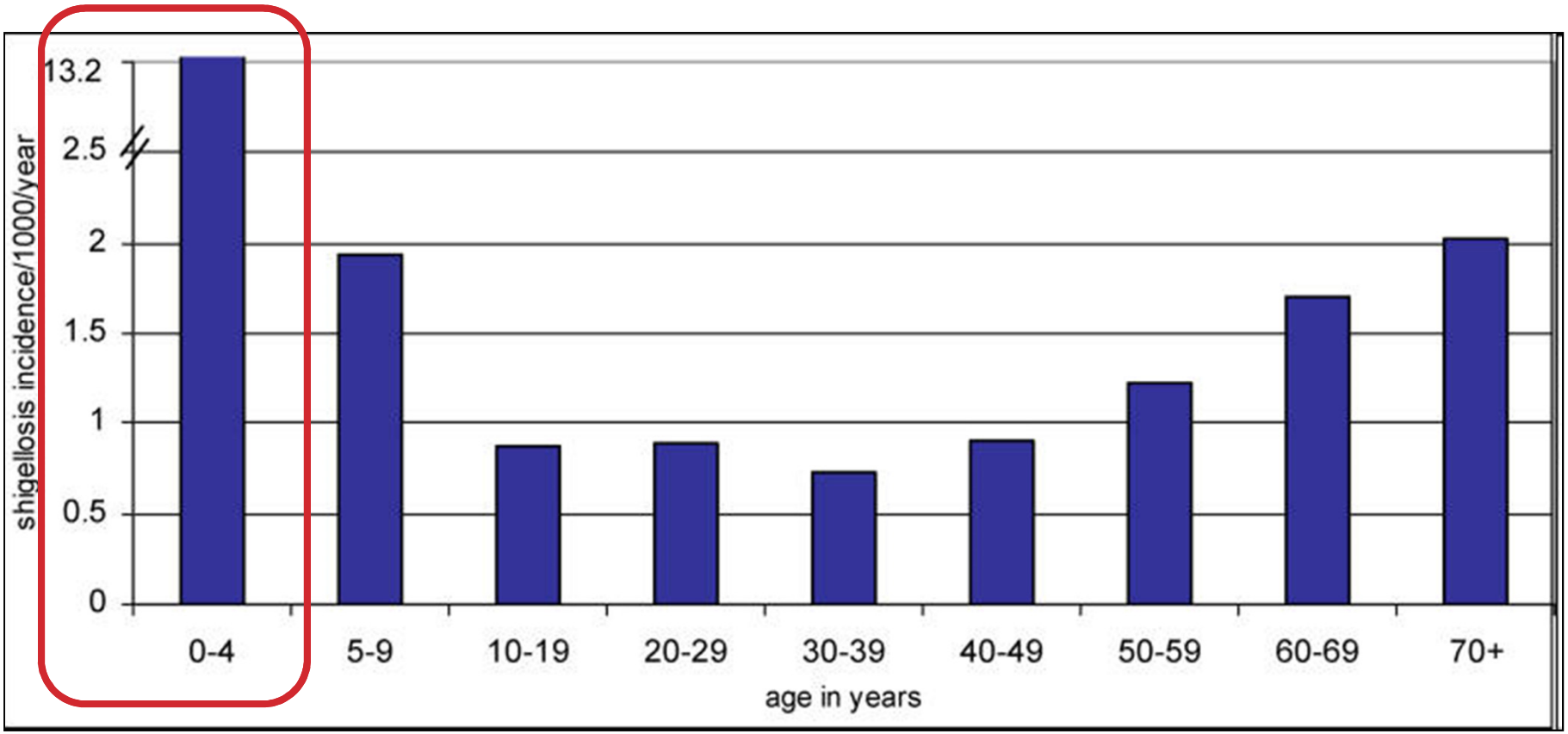
# Shigella



- **Most common cause of acute dysentery worldwide ("Bacillary dysentery")[1]**
- **Global incidence: 80-165 M episodes annually; 700,000- 1M deaths each year [1,2]**
- **99% of infections caused by Shigella occur in developing countries [3]**
- **69% of these episodes and 61% of all deaths attributable to shigellosis occur in children < 5 yrs old [2]**
- **Highest incidence in densely populated areas with unsafe water supply & inadequate sanitation[4]**
- **Outbreaks common in overcrowded, impoverished areas with poor sanitation, inadequate hygiene practices, and unsafe water supplies[1]**

1.WHO. Guidelines for the control of shigellosis, including epidemics due to Shigella dysenteriae type 1. 2005.; 2. Kotloff KL et al. Bull WHO 1999, 77(8):651-666; 3. Ram PK et al. Epidemiol Infect 2008, 136(5):577-603; 4. WHO. Wkly Epidemiol Rec 2005:11

# Overall Shigellosis Incidence by Age Group in Six Asian Countries* (2000-2004)




* **Bangladesh, China, Pakistan, Indonesia, Vietnam &Thailand**

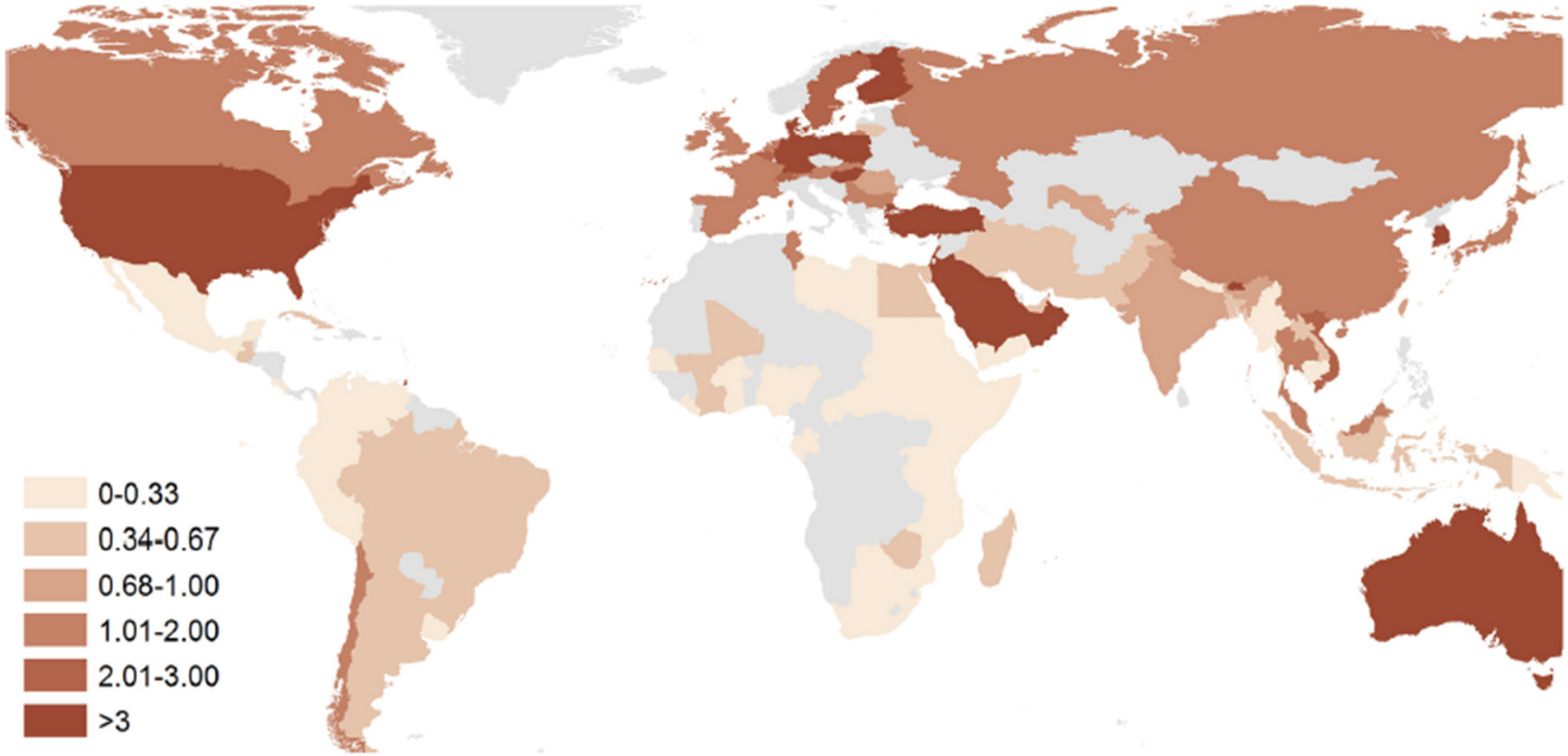
**Note:** **Shigellosis incidence 2.1/1000/y in all age groups;**
**Shigellosis incidence 13.2/1,000/y in 0–4 y age group.**

Von Seidlein L et al. PLoS Med. 2006 September; 3(9): e353.

# The Rising Dominance of *Shigella sonnei*: An Intercontinental Shift in the Etiology of Bacillary Dysentery

Corinne N. Thompson[1,2,3], Pham Thanh Duy[1], Stephen Baker[1,2,3]*

PLOS | NEGLECTED TROPICAL DISEASES | DOI:10.1371/journal.pntd.0003708 June 11, 2015




**Ratio of S. sonnei to S. flexneri isolated**

# Shigellosis

- Incubation period usually < 72 hrs
- Variable severity of illness: mild, self-limited watery diarrhea (~ 50%)→ fulminant dysentery
- Rapid onset of watery stools that becomes bloody after 1-2 days
- Often accompanied by fever, abdominal pain, tenesmus, headache, anorexia
- Increased severity in infants <4 months, malnourished, dehydrated, or recovering from measles
- Mortality 1-10%

# Complications of Shigella Infection

| Intestinal | % |
|---|---|
| Toxic megacolon | 3* |
| Intestinal obstruction | 2.5* |
| Colonic perforation | 1* |
| Proctitis or rectal prolapse | - |

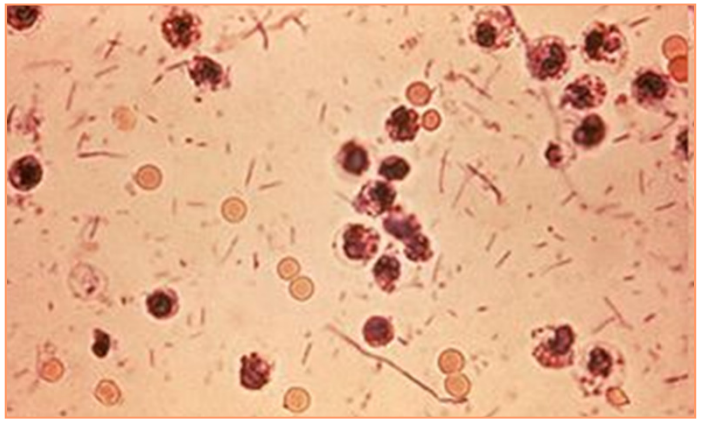
| Systemic | % |
|---|---|
| Bacteremia | 4 |
| Mod to severe hypovolemia | 10-12* |
| Hyponatremia | 29* |
| Leukemoid reaction | 3* |
| Neurologic symptoms | 12-45 |
| Reactive arthritis (Reiter's syndrome) | 1.4 |
| Hemolytic-Uremic Syndrome | <1 |

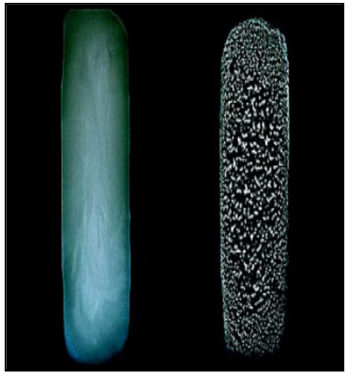
* *Prevalence rates reported for a subpopulation of individuals with Shigella enteritis, and may overestimate true prevalence of the disease.*

Ashkenazi S. Semin Pediatr Infect Dis. 2004;15(4):246.; Ashkenazi S. 

# Diagnosis of Shigella Dysentery

- **Stool microscopy**
  - Numerous PMNs, discrete RBCs; macrophages with ingested RBCs
- **Stool culture**
  - MacConkey agar
  - Xylose lysine desoxycholate agar (XLD), desoxycholate citrate agar
  - Biochemical screening test and serological test for species identification
- **Molecular-based tests**
  - PCR –detect as few 10 cfu in stools





CDC. Laboratory methods for the diagnosis of epidemic dysentery and cholera. WHO/CDS/CSR/EDC/99.8

# Antimicrobial Resistance Pattern for Four *Shigella* Species in 6 Asian Countries

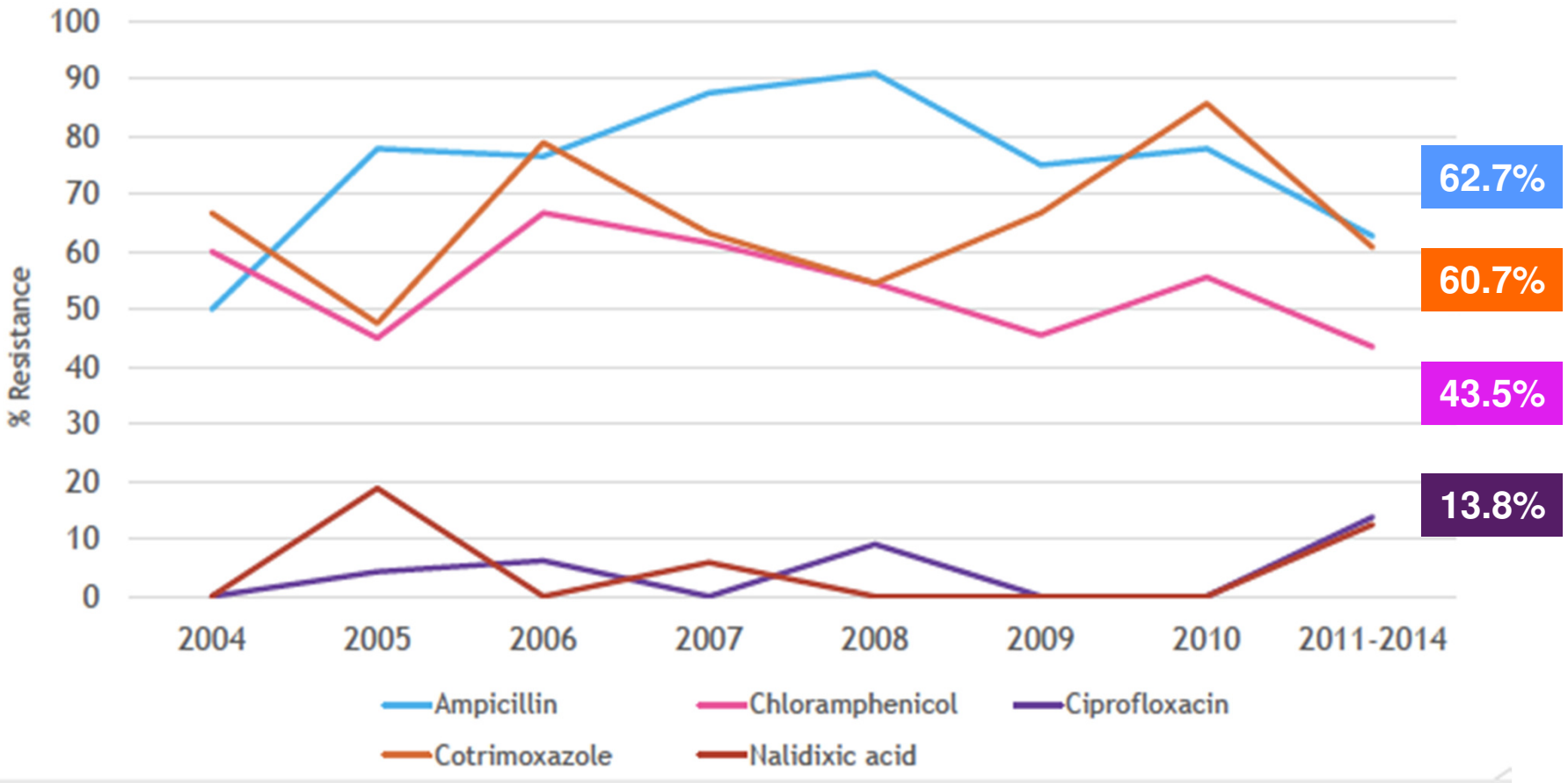
| Antibiotic | *S. flexneri* Serotypes (% of *n*) | | | *S. boydii* (% of *n*) | *S. dysenteriae* (% of *n*) | *S. sonnei* (% of *n*) |
|---|---|---|---|---|---|---|
| | 2a (*n* = 527) | Other (*n* = 1,449) | Total (*n* = 1,976) | (*n* = 189) | (*n* = 110) | (*n* = 652) |
| Ampicillin | 497 (94.3%) | 1,156 (79.8%) | 1,653 (83.7%) | 46 (24.3%) | 41 (37.3%) | 64 (9.8%) |
| Cotrimoxazole | 423 (80.3%) | 1,067 (73.6%) | 1,490 (75.4%) | 91 (48.2%) | 68 (61.8%) | 603 (92.5%) |
| Nalidixic acid | 172 (32.6%) | 301 (20.7%) | 473 (23.9%) | 40 (21.2%) | 9 (8.2%) | 92 (14.1%) |
| Ciprofloxacin | 11 (2.1%) | 20 (1.4%) | 31 (1.6%) | 2 (1.1%) | 0 (0%) | 1 (0.2%) |
| Multidrug-resistant[a] | 8 (1.5%) | 10 (0.7%) | 18 (0.9%) | 0 (0%) | 0 (0%) | 0 (0%) |

* **Bangladesh, China, Pakistan, Indonesia, Vietnam &Thailand**

**Resistance of *Shigella* isolates to the first line drugs: ampicillin 10-80%; cotrimoxazole 48-92%; nalidixic acid 8-24%**

von Seidlein L et al. PLoS Med. 2006 September; 3(9): e353.

# Percent Resistance of *Shigella spp.*
## DOH-ARSP 2004-2014

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# Antimicrobial Therapy of Shigellosis in Developing Countries

| Drug | Cost & Availability | Dose |
|---|---|---|
| **Preferred agent** | | |
| **Ciprofloxacin** | **Expensive Moderately available** | **Children:** 30 mg/kg/day (divided twice daily) for 3-5 days**;** **Adults:** 500 mg 2x a day x 3-5 days |
| **Alternative agents** | | |
| **Azithromycin** | **Expensive Moderately available** | **Children:** 10-20 mg/kg once a day x 5 days; **Adults:** 500 mg once a day x 5 days |
| **Ceftriaxone** | **Expensive Moderately available** | **Children:** 50 mg/kg IV once daily for 5 days**;** **Adults:** 1g IV once daily for 5 days |
| **Pivmecillinam (Amdinocillin pivoxil)** | **Expensive Limited** | **Children:** 20 mg/kg 3 - 4x a day x 5 days; **Adults:** 400 mg 2-3 x a day x 5 days |

*WHO.. Guidelines for the control of shigellosis, incuding epidemics due to Shigella dysenteriae 1. World Health Organization, Geneva 2005.*

# Safety of FQ in Children

- **FQ are not recommended for routine use in children <18 years of age because of animal studies demonstrating development of arthropathy and cartilage erosions in weight-bearing joints [1]**
- **Arthropathy not seen in humans over the past decades of FQ use [1-6]**
- **No clinically detectable difference in development of musculoskeletal AE during 1-5 years of follow-up in children who received FQ or a comparator in RCTs [7]**
- **In some children, the benefit of quinolones outweighs any small short-term risk of joint toxicity [1-6]**
- **AAP recommends use of fluoroquinolones in children be limited to the treatment of infections for which no safe and effective alternative exists [1]**

1.Bradley JS, Jackson MA, Committee on Infectious Diseases AAP. Pediatrics 2011; 128:e1034; 2. Burkhardt JE et al. Clin Infect Dis 1997; 25:1196; 3. AAP Red Book 2015. p.871;4. Orenstein DM, et al. Clin Pediatr (Phila) 1993; 32:504; 5. Sendzik J et al. Int J Antimicrob Agents 2009; 33:194; 6. Pichichero ME et al. Clin Infect Dis 2005; 41:470; 7. Bradley JS, et al. Pediatrics 2014; 134:e146.;8. Yee CL et al. Pediatr Infect Dis J. 2002; 21(6): 525-9.

# Antimicrobials Not Effective Against Shigella

- Metronidazole
- Streptomycin
- Tetracyclines
- Chloramphenicol
- Sulfonamides
- Nitrofurans (e.g. nitrofurantoin, furazolidone)
- Aminoglycosides (e.g. gentamicin, kanamycin)
- First and second generation cephalosporins (e.g., cephalexin, cefamandole)

# Typhoid Fever

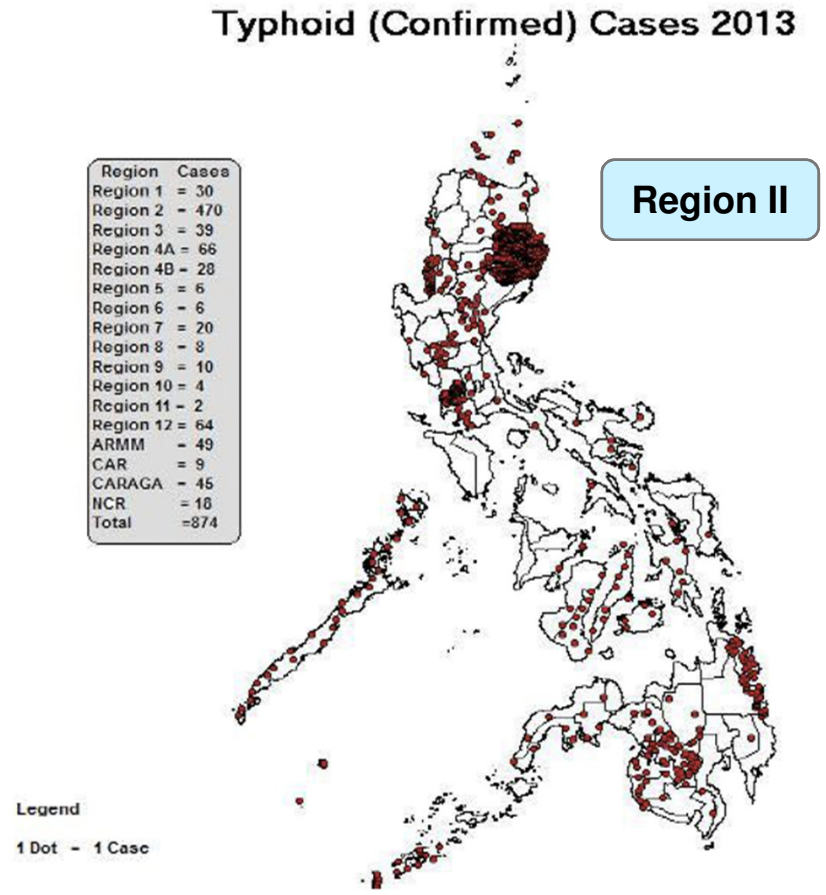
- Etiologic agent: *S. enterica serotype typhi* (formerly *S. typhi)*
- Global: 16-33 M cases; 500,000-600,000 deaths annually
- High incidence areas (> 100 cases/ 100,000 person years): South-central Asia, SE Asia, and southern Africa
- More common in children 5-19 years old and in young adults
- Prevalent in impoverished areas, with overcrowding and poor access to sanitation
- Transmitted by contaminated food and water
- Grossly bloody stools (10-20%) results from intestinal perforation and hemorrhage
- Due to ileocecal lymphatic hyperplasia and erosion of blood vessels of the Peyer's patches; usually 2nd-4th wk of illness

Misra S et al. Clin Infect Dis 1997; 24:998; Crump JA. Bull WHO 2004; 92:

# Confirmed Typhoid Cases in the Philippines, 2013

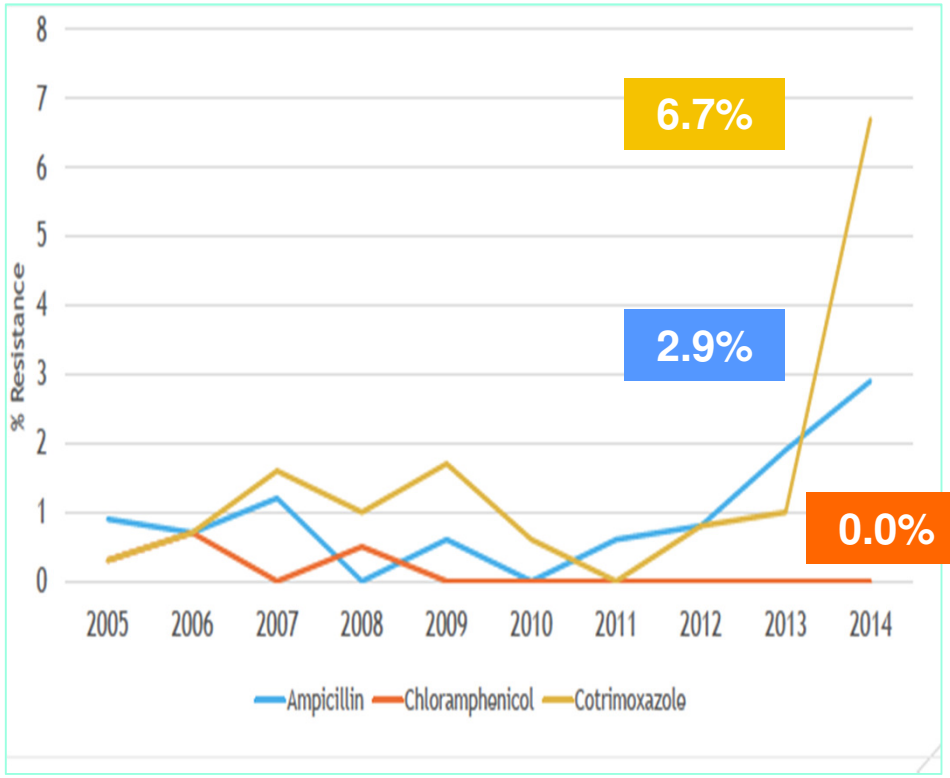
| Age Group (yrs) | Cases | Deaths (CFR%) |
|---|---|---|
| < 1 | 13 | 0.00 |
| 1- 4 | 169 | 0.00 |
| 5-14 | 325 | 0.00 |
| 15-24 | 154 | 0.00 |
| 25-39 | 110 | 1 (0.91%) |
| 40-64 | 84 | 1(0.19%) |
| ≥65 | 19 | 0.00 |
| TOTAL | 874* | 2 (0.23%) |

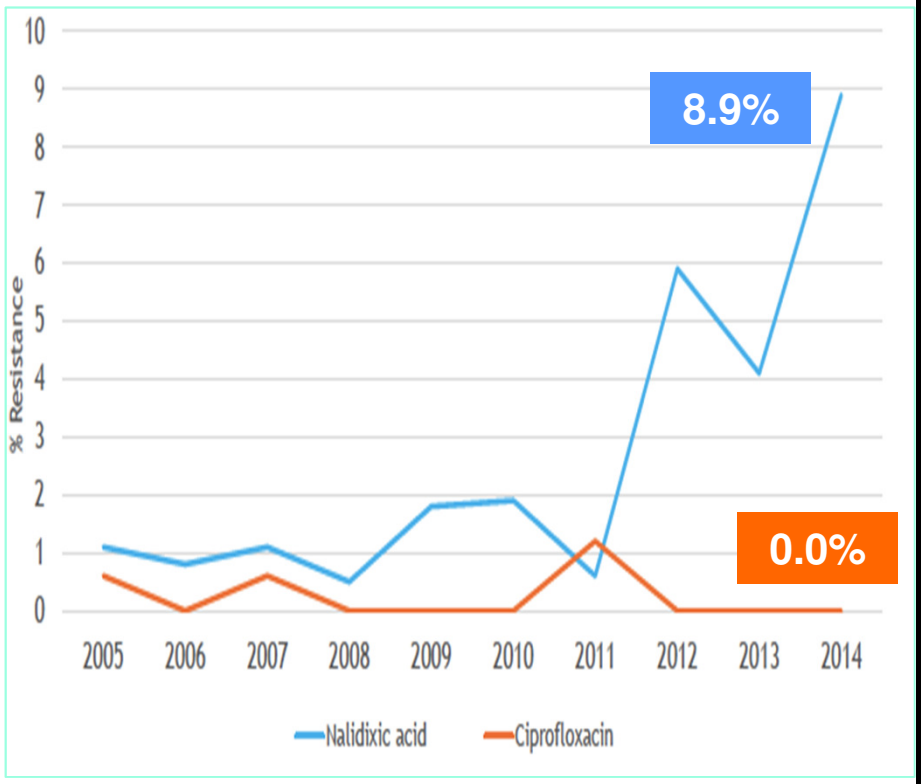
*Out of 14,726 probable TF cases




PIDSR Annual Report 2013. DOH-NEC

# Yearly Ampicillin, Chloramphenicol and Cotrimoxazole Resistance Rates of *Salmonella typhi*, ARSP, 2005-2014

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# Nontyphoid Salmonella

- Causes 1-5% of gastroenteritis in most developing countries
- Infection usually results from ingestion of undercooked poultry, contact with pets (reptiles)
- Incubation period 8-24 hrs after ingestion of infective dose
- Enterotoxin-mediated watery diarrhea, nausea, vomiting, fever, and abdominal cramping; occasionally bloody
- Severe illness, bacteremia, and dissemination more likely in infants, elderly persons, those with impaired immune systems
- *Salmonella choleraesuis* and *Salmonella heidelberg - invasive*
- *S. typhimurium* - antibiotic resistant strains; increase in risk of bacteremia

# Diagnosis of Salmonella Infections

- **Culture:**
  - Stool, blood, bone marrow, urine
  - McConkey, Salmonella-Shigella agar, Bismuth sulfate agar
  - Serotyping to identify individual serotypes

- **Serology: Particle agglutination slide tests, CIE, RIA, ELISA**
- **Molecular-based: DNA hybridization, PCR**

# Antimicrobial Treatment of Non-typhoidal Salmonella

- ***Onwuezobe IA, Oshun PO, Odigwe CC. Antimicrobials for treating symptomatic non-typhoidal Salmonella infection. Cochrane Database of Systematic Reviews 2012;11:CD001167.***

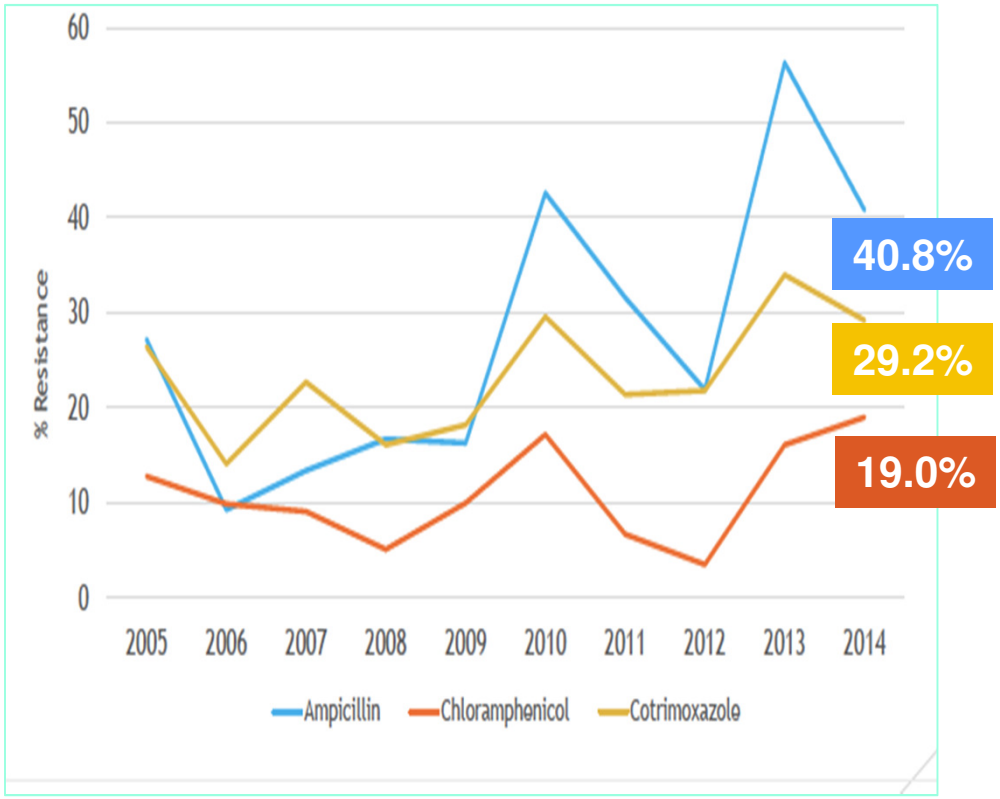
- **Main Results:**
  - Antibiotics not usually beneficial in healthy individuals; may result in persistent colonization and spread of resistant bacterial strains.
  - No significant differences in duration of illness and diarrhea between those given any antibiotic and those given placebo/no treatment group.
  - Those receiving antibiotics were almost twice as likely to have relapse with the same Salmonella serovar one month after treatment (RR 1.96, 95% CI 1.29 to 2.98) and non-severe adverse drug reactions (OR 1.67, 95% CI 1.05- 2.67)

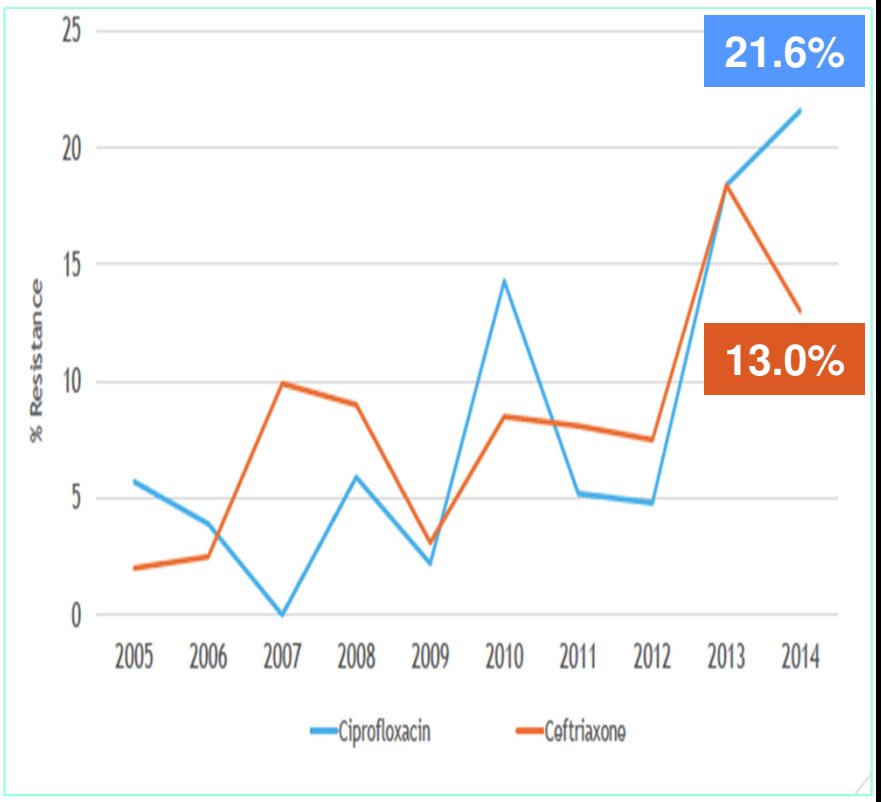
# Antimicrobial Treatment of Non-typhoidal Salmonella

- **Antibiotics indicated only in severe cases and those at high risk for invasive diarrhea :**
  - Individuals with severe illness (high or persistent fever, very frequent bowel movements, need for hospitalization)
  - Infants <12 months
  - Adults >50 years
  - HIV-infected patients
  - Immunocompromised patients
  - Individuals with cardiac, valvular, endovascular abnormalities or substantial joint disease

1. Geme JW et al. Pediatr Infect Dis J 1988; 7:615; 2. AAP Red Book 2015 Report of the Committee on Infectious Diseases, 2015. p.695.; 3. Benenson S et al. Am J Med 2001; 110:60; 4. Cohen PS et al. Ann Intern Med 1978; 89:931; 5. Gordon MA.. J Infect 2008; 56:413; 6.Gordon MA et al. AIDS 2002; 16:1633.

# Yearly Resistance Rates of Nontyphoidal *Salmonellae* ARSP, 2005-2014

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# Antimicrobial Treatment of TF and Non-typhoid Salmonella Infections

- **Susceptible Salmonella infections**
  - Amoxicillin 100mg/kg/day (max 6g/day) x 14 days
  - TMP-SMX 8 mg T/kg/day in 2 divided doses x 14 days
  - Chloramphenicol 100mg/kg/day (max 4g/day) x 14 days
- **Drug-resistant Salmonella and Nontyphoidal Salmonella**
  - Third generation cephalosporins: ceftriaxone, cefoperazone, cefotaxime, cefixime
  - Fluoroquinolones: ciprofloxacin, ofloxacin
  - Azithromycin
  - Aztreonam
  - Carbapenems: Imipenem, meropenem

# Classification of *E. coli* Associated with Diarrhea

| E. coli strain | Pathogenic Mechanism | Type of Diarrhea |
|---|---|---|
| Enteropathogenic **(EPEC)** | Small bowel adherence & effacement | Acute & chronic endemic & epidemic watery diarrhea |
| Enterotoxigenic **(ETEC)** | Small bowel adherence and effacement; HS/HL enterotoxin | Infantile diarrhea & traveler's diarrhea; watery |
| Enteroaggregative **(EAEC)** | Small & large bowel adherence; enterotoxin & cytotoxin | Acute & chronic watery diarrhea, occasionally bloody |
| Enteroinvasive **(EIEC)** | Large bowel adherence, invasion & inflammation | nonbloody or **bloody diarrhea** |
| Enterohemorrhagic/Shiga toxin producing **(STEC)** | Large bowel adherence & effacement; Shiga-like toxin | Hemorrhagic colitis; nonbloody or **bloody diarrhea** |

# *Enteroinvasive E. coli* (EIEC)

- Cause sporadic food-borne outbreaks in adults and children
- Transmission through consumption of contaminated foods, such as raw or undercooked ground meat products, raw milk and contaminated raw vegetables and sprouts
- Incubation period: 10 hrs to 6 days
- EIEC penetrate and multiply within colonic epithelial cells
- Symptoms of illness similar to shigellosis: febrile diarrhea, watery or bloody (dysentery)
- Diagnosis requires specialized techniques including serotyping, tissue culture, immunochemical test and DNA hybridization

# *Enterohemorrhagic E. coli* (EHEC)

- Strains capable of producing Shiga toxin; typically cause bloody diarrhea
- Cause sporadic food-borne outbreaks from raw or undercooked ground meat, raw seed sprouts, unpasteurized milk, water or produce contaminated with bovine feces
- Incubation period: 1-8 days (ave 3-4 days)
- Shiga-like toxin responsible for vascular damage, edema, diffuse bleeding in the colon (hemorrhagic colitis)
- "Hamburger diarrhea" – initially nonbloody, progressing to bloody diarrhea, associated with abdominal pain & fever

# Shiga toxin-producing E. coli (STEC)

- Shiga-like toxin - inhibit protein synthesis, damage epithelial cells, cause vascular necrosis and edema of intestinal tract (hemorrhagic colitis)
- Absorption and systemic complications:
  - Hemolytic-uremic syndrome (HUS)
  - Post-diarrheal thrombotic thrombocytopenic purpura (TTP)
- Type O157:H7 - most virulent; predominant cause of HUS
- Type O104:H4 - new STEC strain identified as the cause of an outbreak of bloody diarrhea and HUS in Germany and 15 other countries in Europe
- Diagnosis confirmed by serotyping sorbitol-negative E. coli isolates or by using tissue culture or gene probes to detect cytotoxin

# Hemolytic-Uremic Syndrome (HUS)

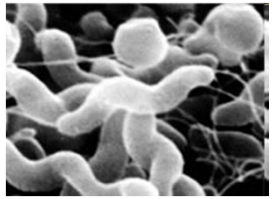
- **HUS represents toxin-mediated endothelial cell injury resulting in altered vasculature and thrombi formation**
- **TRIAD: Hemolytic anemia, thrombocytopenia, renal failure**
- **More common in children < 4 years old**
- **Develop within 2 weeks after onset of diarrhea**
- **Etiology:**
  - **Common:** *E. coli* O157:H7 (~5-10%); *S. dysenteriae type 1*
  - **Less common:** *Salmonella, Campylobacter, Bartonella*, viruses (e.g. coxsackie, ECHO, influenza, EBV)
- **Management: dialysis; anticoagulants; plasmapharesis or FFP**
- **Prognosis: aggressive management of ARF ~ 90% recover renal function; 10-30% CRD; 3-5% mortality**

# Antimicrobial therapy for Bloody Diarrhea due to E. coli

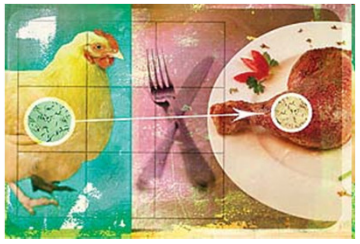
- **EIEC - Antimicrobials for Shigella probably effective; ideally based on susceptibility testing**
  - TMP-SMX, azithromycin, ciprofloxacin
- **EHEC - Antibiotic therapy is generally not beneficial**
  - Treatment of EHEC infection consists of supportive care and monitoring for the development of microangiopathic complications, such as HUS.
- **STEC – no increased benefit for treating with antibiotics; may increase risk for HUS due to ↑toxin**
  - Antibiotic use during E. coli O157:H7 infections is associated with a higher rate of subsequent HUS and should be avoided (36% vs 12%; p = 0.001).
  - Exposure to antibiotics during the first week of onset of illness was associated with development of HUS (aOR 3.62; 95% CI, 1.23-10.6).

Wong et al. Clin Infect Dis. 2012;55(1):33.

# Campylobacter Infection



- Principal cause of human Campylobacter enteritis: *Campylobacter jejuni, Campylobacter coli*
- Estimated incidence: 400 million per year
- Common in < 5 yrs old, causes 5-15% of diarrhea in infants
- Most children acquire immunity during first year of life, usually self-limited diarrhea
- Some present with severe watery diarrhea, frank dysentery with acute colitis, bloody diarrhea, toxic megacolon
- Bacteremia and severe disease more common in immunocompromised
- Pathology: direct invasion, cytotoxin & heat-labile enterotoxins
- Outbreaks commonly associated with ingestion of uncooked meat or poultry, contaminated water, unpasteurized milk
- Diagnosis: Selective culture media (CampyBAP, Blaser or Skirrow's media); Darkfield microscopy; with phase contrast exam of stools; serology; PCR



# Postinfectious Complications of Campylobacter infection

- **Reactive arthritis or Reiter's syndrome**
  - Occurs in approx 2-7% of Campylobacter infections
  - affects large weight-bearing joints (knees, lower back)
  - persons who have HLA-B27 are genetically predisposed

- **Guillain-Barre syndrome (GBS)**
  - Reported in 1 per 1000-3000 Campylobacter infections
  - begins several weeks after the diarrheal illness

- **Miller Fisher Syndrome (MFS)**
  - neurological syndrome affecting nerves
  - Associated with ataxia, ophthalmoplegia, nonreactive pupils

Adedayo O & Kirkpatrick B. Hospital Physician 2008;9-15

# Antimicrobials for Campylobacter jejuni

- **Antimicrobials generally not required** [1,2]
  - Self-limiting; many asymptomatic by time diagnosis established and do not require treatment
- **Antimicrobials reserved for immmunocompromised, severe symptoms (bloody stools, high fever, extraintestinal infection) and worsening or prolonged symptoms lasting one week** [1-3]
  - Children: Azithromycin 10 mg/kg for 3 days or
    Erythromycin 10 mg/kg every 6 hrs for 5 days
  - Adults: Levofloxacin 500 mg once daily or
    Ciprofloxacin 750 mg every 12 hrs for 3-5 days
    Azithromycin 500 mg once daily for 3 days
- **Bacteremia:** Carbapenem, 3rd or 4$^{th}$ gen Cephalosporin, aminoglycoside [4]

1. Ruiz-Palacios GM. Clin Infect Dis 2007; 44:701; 2. Kuschner RA Clin Infect Dis 1995; 21:536; 3. Ternhag A. Clin Infect Dis 2007;44: 696-700; 4. AAP 2012 Red Book

# *Yersinia enterocolitica*

- **Gram-negative bacteria found in birds, farm and domestic animals**
- **Epidemics related to contaminated water, milk & milk products, consumption of undercooked or raw pork products**
- **Incubation period: 3-7 days**
- **Bloody diarrhea - 25-50%; associated with necrosis of the Peyer's patches, chronic lymphadenopathy, hepatic and splenic abscesses**
- **Bloody diarrhea more frequent in children than adults**
- **Infection may mimic appendicitis ("pseudoappendicitis" )**
- **Diagnosis requires culture isolation using selective culture media Cefsulodin-irgasan-novobiocin agar plates; serology; PCR**

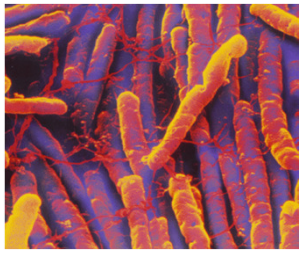
1.Tacket CO et al. JAMA 1984; 251:483; 2.Tacket CO et al. Am J Epidemiol 1985; 121:705 ;3. Lee LA et al. N Engl J Med 1990; 322:984; 4. Cover TL & Aber RC. N Engl J Med 1989; 321:16.

# Antibiotic Treatment for *Yersinia enterocolitica*

- **Most cases of *Yersinia* enterocolitis are self-limited**
- **No evidence of clinical benefit in treatment of acute, uncomplicated yersiniosis with antibiotics**
- **Antibiotics reserved for those with severe disease or have underlying comorbid illness.**
  - Complicated GI infections or focal extraintestinal infections: ciprofloxacin, doxycycline, trimethoprim-sulfamethoxazole for 5 days
  - Septicemia or severe disease: 3rd gen Cephalosporins OR ciprofloxacin + aminoglycoside for 3 weeks

1. Gayraud M et al. Clin Infect Dis 1993; 17:405; 2. Black RE & Slome S. Infect Dis Clin North Am 1988; 2:625.

# *Clostridium difficile*



- **Important cause of antibiotic-associated diarrhea[1-3]**
- **Commonly healthcare-associated infection but with increasing reports of community-associated *C.difficile* infection [1-3]**
- **Clinical spectrum of *C. difficile* infection ranges from asymptomatic colonization to fulminant colitis[4]**
- **Common manifestations: fever, abdominal tenderness, profuse, watery diarrhea; bloody stools found in 10-25% percent of children with *C. difficile* infection [5,6]**
- **Pseudomembranous colitis - Onset during or within 21 days after administration of antibiotic**
- **Laboratory testing for *C. difficile* infection involves detection of *C. difficile* toxin(s) or toxigenic *C. difficile* organisms in a stool specimen**

1. Kim KH et al. J Infect Dis 1981; 143:42; 2. Zilberberg MD et al.. Emerg Infect Dis 2010; 16:604; 3. Deshpande A et al. Pediatr Infect Dis J 2013; 32:1138; 4. Lessa FC et al. N Engl J Med 2015; 372:825; 5. Crews JD et al. Pediatr Infect Dis J 2014; 33:924; 6. Zwiener RJ et al. Pediatr Infect Dis J 1989; 8:876.

# Management of Clostridium difficile infection in children

- **Discontinuation of inciting antibiotics [1-3]**
  - Reduce duration of symptoms and recurrence
  - May be sufficient in resolution of symptoms
- **Correction of fluid losses and electrolyte imbalances**
- **Antibiotic therapy for persistent disease despite discontinuation of inciting antibiotics or with moderate to severe disease [4]**
  - Profuse diarrhea
  - Abdominal pain and tenderness
  - Abdominal distention
  - Pseudomembranous colitis
  - Hypotension
  - Ileus
  - Shock
  - Toxic megacolon

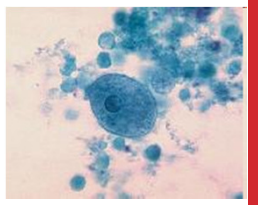
1.Schutze GE and Committee on Infectious Diseases, AAP. Pediatrics 2013; 131:196; 2. Cohen SH et al. Infect Control Hosp Epidemiol 2010; 31:431; 3. Surawicz CM et al. Am J Gastroenterol 2013; 108:478.; 4. Schutze GE et al. Committee on Infectious Diseases, AAP. Pediatrics 2013; 131:196.

# Antibiotic Therapy for C. difficile-associated Diarrhea

- **Mild to moderate disease** [1-3]
  - Metronidazole 30 mg/kg per day by mouth in four divided doses (maximum 500 mg/dose) for 10-14 days
- **Severe or complicated disease** [4-5]
  - Vancomycin is 40 mg/kg per day by mouth in four divided doses (maximum 125 mg/dose) for 10-14 days
  - Oral formulation more expensive; vancomycin powder for injection may be reconstituted and used for oral administration [5]
- **Inability to tolerate oral therapy** [5]
  - IV Metronidazole 40 mg/kg per day in 4 divided doses (maximum 500 mg/dose) in combination
  - ± Rectal instillation of Vancomycin (500 mg/100 mL normal saline):
    - < 10 years 50-75ml ; ≥10 years 100 mL administered by retention enema four times daily (Caution – rectal perforation)

1. Vasa CV.. Am J Gastroenterol 2003; 98:354; 2. Wenisch C et al. Clin Infect Dis 1996; 22:813; 3. .Zar FA et al. Clin Infect Dis 2007; 45:302; 4. Schutze GE, Committee on Infectious Diseases, AAP. Pediatrics 2013; 131:196; 5. Cohen SH et al. Infect Control Hosp Epidemiol 2010; 31:431; 6. Sammons JS et al. Pediatric Infect Dis Soc 2013; 4:43.

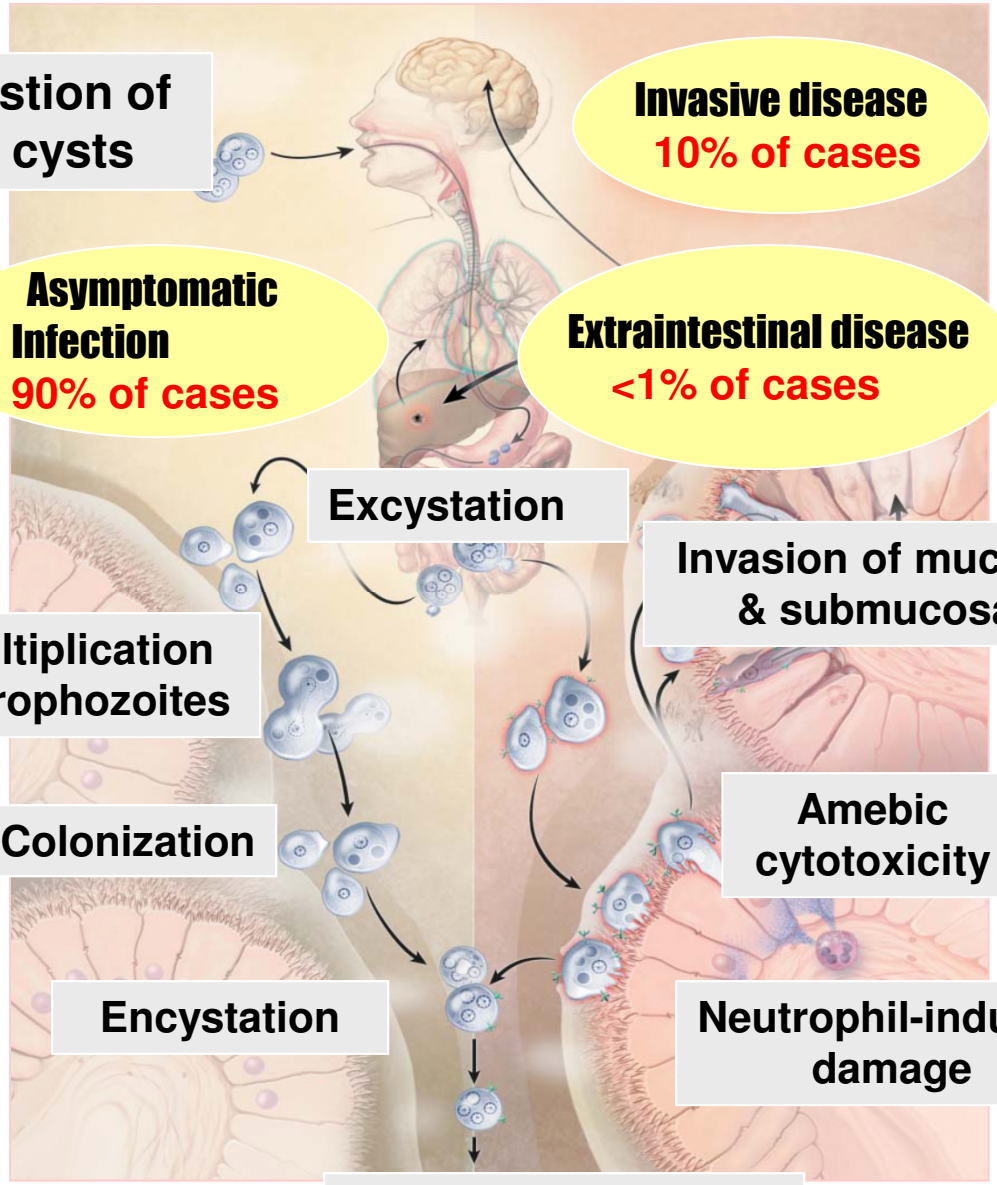
# *Entamoeba histolytica*

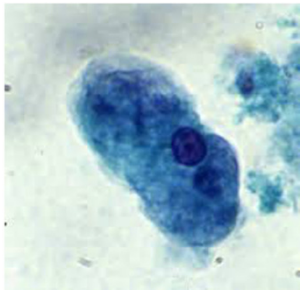


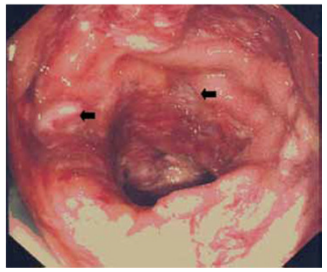
- **Amebiasis - a parasitic disease of worldwide public health importance [1,2]**
- **Global prevalence: 40-50 M people infected with *E. histolytica* develop amebic colitis or extraintestinal abscesses; approx. 100,000 deaths a year [1-4]**
- **High rates of amebic infection in Asia, the sub-Saharan and tropical regions of Africa, Central and South America [4]**
- **Seroprevalence rates of amebiasis in developing countries: 5% to 64%**
- **In the Philippines, variable prevalence rates depending on geographic area, study population, diagnostic method:**
  - Stool microscopy: 0-8% [5,6]
  - IHA: 1-13% [5]
  - PCR: 0-65.5% [7,8]
- **Infection commonly acquired by ingestion of food or water contaminated with *E. histolytica* cysts**

1. Walsh JA. Rev Infectious Dis 1986; 8: 228-38;2. WHO/PAHO/ UNESCO Wkly Epidemiol Record 1997; 72: 97-9**; 3.** Li et al. Gastroenterology Clinics 1996; 25: 471-92; 4. Petri WA et al. Parasit Today 2000; 16: 320-1; 5. Cross J. Phil J Microbiol Infect Dis 1980; 9(1):21-26; 6. Salazar NP. Phil J Microbiol Infect Dis 1990; 19(23):57-60; 7.Rivera WL. Ann Trop Med Parasitol 1998; . 59(6): ,916-921;8. Rivera WL. Parasitol Res. 2006;98(2):106-10

# Pathogenesis of Amebiasis



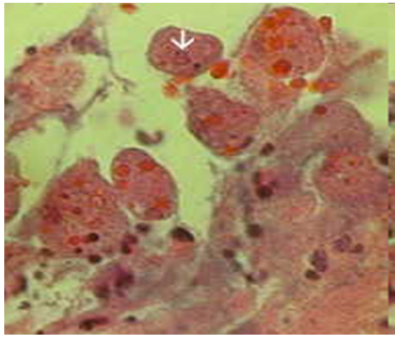


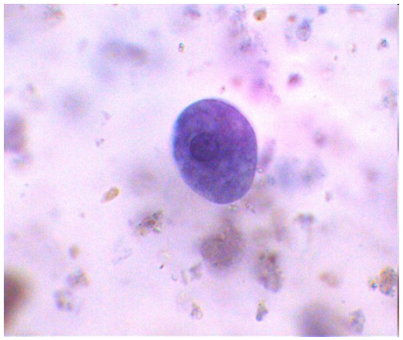
Haque et al. NEJM 2003; 348;1567

# Clinical Forms of Amebic Colitis

- **Amebic dysentery**
  - diarrhea with visible blood and mucus
  - (+) *E. histolytica* trophozoites with ingested red blood cells (Hematophagous trophozoite) in stools or tissues
  - sigmoidoscopic examination: inflamed mucosa with or without discrete ulcers

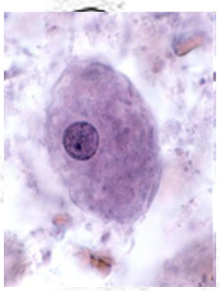
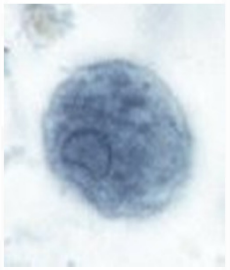
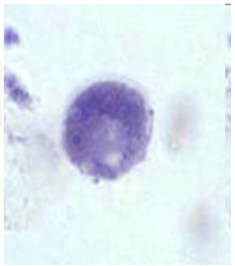
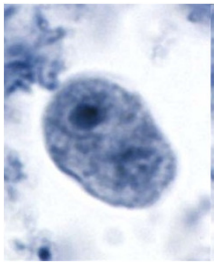
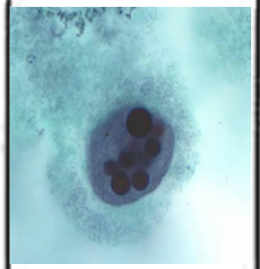
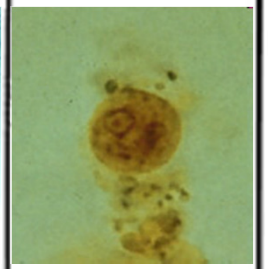
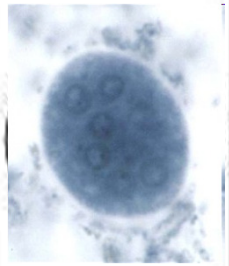
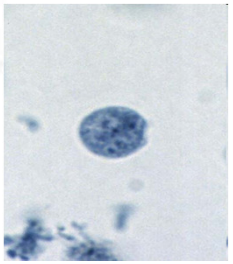
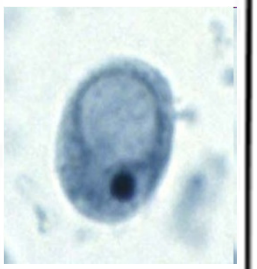
- **Nondysenteric amebic colitis**
  - recurrent bouts of diarrhea w/ or w/o mucus but no visible blood
  - (+) *E. histolytica* cysts or trophozoites with no ingested red blood cells (Nonhematophagous trophozoite) in stools
  - sigmoidoscopic examination: normal





WHO Expert Committee on Amoebiasis, 1969

# Structure of Human Ameba

| | Amebae | | | | | |
|---|---|---|---|---|---|---|
| | ***Entamoeba histolytica*** | *Entamoeba hartmanni* | *Entamoeba coli* | *Entamoeba polecki** | *Endolimax nana* | *Iodamoeba bütschlii* |
| Trophozoite |  |  |  |  |  |  |
| Cyst |  |  |  |  |  |  |

*Rare, probably of animal origin

# Comparison of Different Diagnostic Tests for Amebiasis

| Test | Specimen | Sensitivity (%) | | Specificity (%) |
|---|---|---|---|---|
| | | Amebic colitis | Amebic Liver abscess | |
| Microscopy | Stool | 25-60 (85-95 if +rbc | <10 | 10-50 |
| | ALA fluid | NA | <25 | 100 |
| Culture and Isoenzyme | Stool | 50-70 | <25 | Gold standard |
| Antibody detection | IgM, acute | 75-85 | 70-100 | >85 |
| | IgG, convalescent | >90 | >90 | - |
| Antigen Detection (ELISA) | Stool | >95 | Usually (-) | >95 |
| | Serum | 65 | 75-100 | >90 |
| | ALA fluid | NA | 100 | 90-100 |
| PCR-based assays | Stool | >90 | NA | >90 |
| | ALA fluid | NA | 100 | 90-100 |

Fotedar et al. Clin Microbiol Rev 2007; 20:511-532

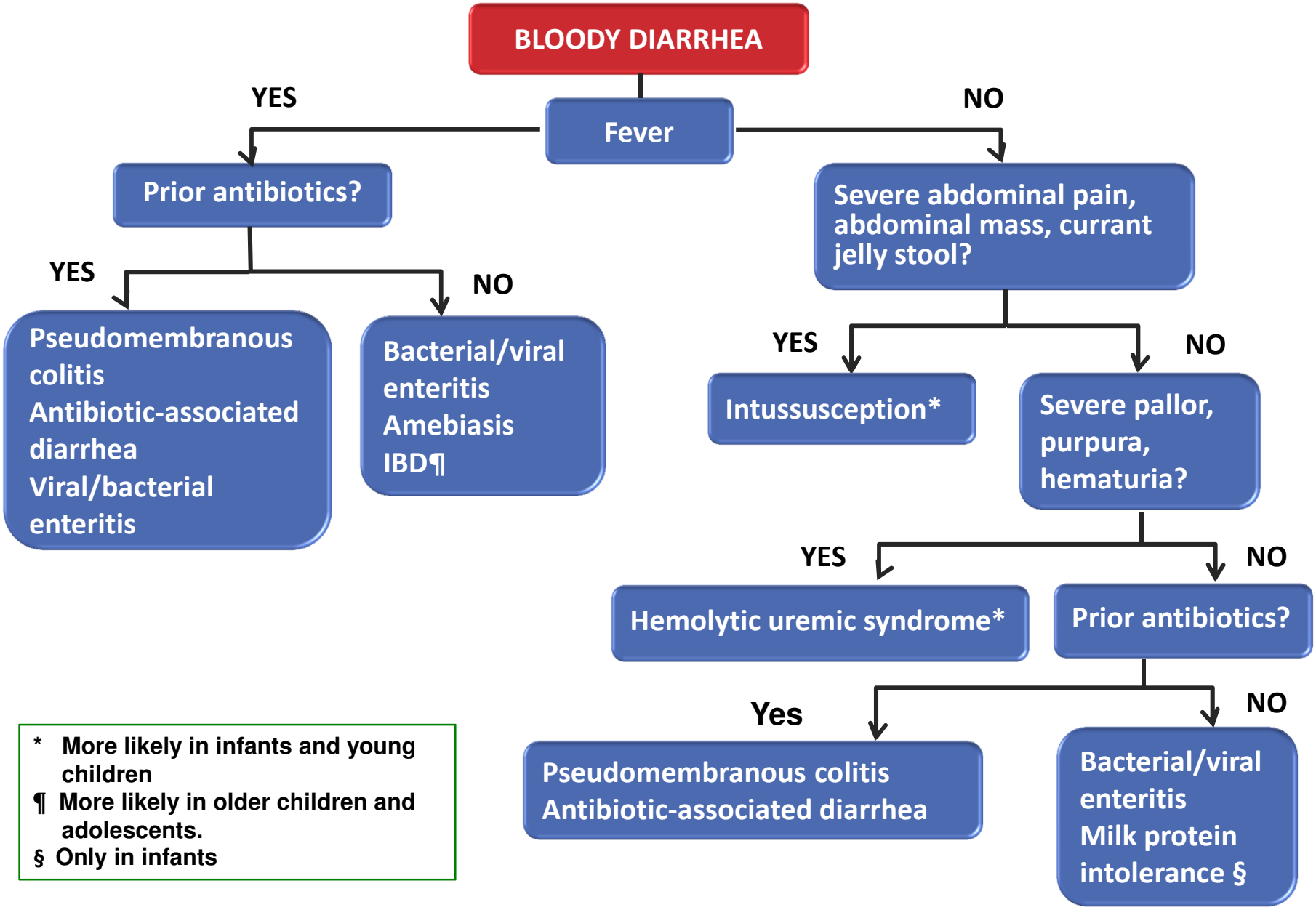
# Drug Treatment of Amebic Colitis

- **Tissue Amebicide – for treating invasive amebiasis**
  - Drug of Choice: Metronidazole 35-50mg/kg/day in 3 doses x 7-10 days
  - Alternative: Tinidazole 50 mg/kg/day (max 2 g) OD x 3 days

- **Luminal agents - recommended after giving a tissue amebicide**
  - Diloxanide furoate 20 mg/kg/day in 3 doses x 10 days
  - Paromomycin 25-35 mg/kg/day in 3 doses x 10 days
  - Iodoquinol 30-40 mg/kg/day in 3 doses x 20 days

AAP. 27th ed. 2006; WHO. Bull WHO 1985; WHO Geneva 1994; WHO. 4th ed. Geneva 2005; The Medical Letter. 2004; WHO Drugs used in parasitic diseases. 2nd ed. Geneva: WHO 1995; WHO/PAHO/ UNESCO Wkly Epidemiol Record 1997 Haque R et al. NEJM 2003; Petri et al, Parasitol Today 2000; Reed SL, Clin Infect Dis 1992; Stanley. Lancet 2003

# EVALUATION OF ACUTE BLOODY DIARRHEA IN A CHILD




* More likely in infants and young children
¶ More likely in older children and adolescents.
§ Only in infants

Modified from Fleisher G. Evaluation of diarrhea in children. ©2016 UpToDate

# Four Principal Steps in the Management of Children with Bloody Diarrhea

- **F - Fluids**
  - Prevent dehydration with oral or IV rehydration fluids
- **F - Follow-up**
  - Re-evaluate clinical status after 48 hrs
- **F - Feeding**
  - Continue provision of nutritious food: breastfeeding; small frequent meals
- **A - Antimicrobial therapy**
  - Antimicrobial treatment should be based on suspected or identified specific bacterial pathogen

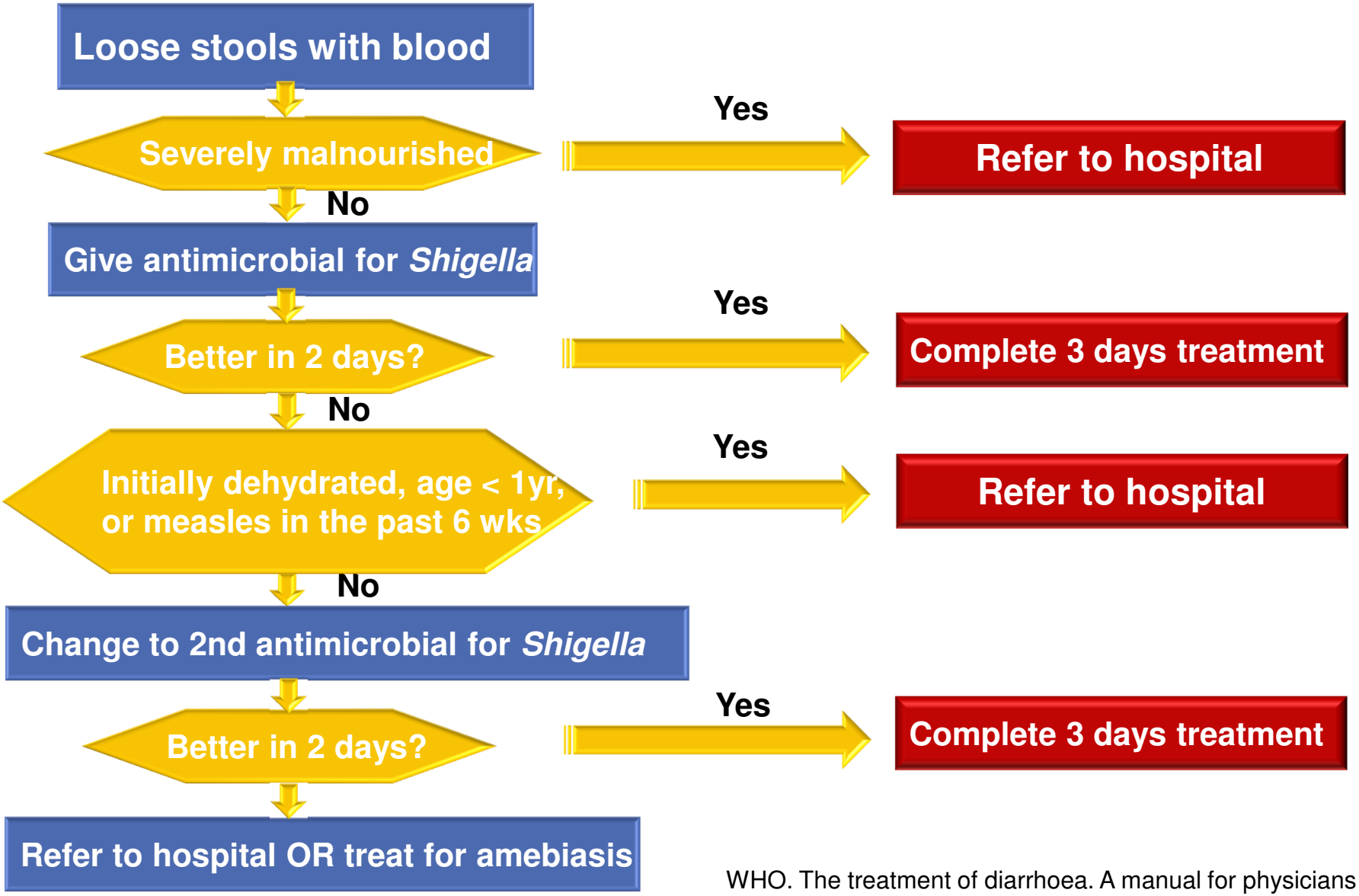
WHO. The Management of Bloody Diarrhoea in Young Children. WHO/CDD/94.49

# Antimicrobial Therapy of Bloody Diarrhea in Infants & Children

- **Rationale for antimicrobial therapy against *Shigella***
  - Shigella is the most frequent cause of bloody diarrhea in this age group
  - Epidemics of bloody diarrhea are essentially caused by *Shigella dysenteriae* type
  - Shigellosis is more likely than other causes of diarrhea to result in complications and death if effective antibiotic therapy is not given promptly
  - Early treatment of shigellosis with an effective antibiotic substantially reduces risk of severe morbidity

WHO. The Management of Bloody Diarrhoea in Young Children. WHO/CDD/94.49

# Outpatient Management of Bloody Diarrhea in Children < 5 yrs of age




WHO. The treatment of diarrhoea. A manual for physicians and other senior health workers WHO/FCH/CAH/05.1

# Metronidazole - NOT First-line drug for Bloody Diarrhea!

- **Amebiasis is an *unusual* cause of bloody diarrhoea in young children, usually causing less than 3% of episodes**
- **Young children with bloody diarrhea should not be treated routinely for amebiasis**
- **Metronidazole - no efficacy against *Shigella* or other invasive bacteria**
- **Anti-amebic treatment should be considered at *any time* when:**
  - microscopic examination of fresh feces done in a reliable laboratory reveals trophozoites of *E. histolytica* containing red blood cells
  - two different antimicrobials usually effective for *Shigella* in the area have been given without clinical improvement
  - Outbreak of amebiasis in the community

WHO. The Management of Bloody Diarrhoea in Young Children. WHO/CDD/94.49; The treatment of diarrhoea. A manual for physicians and other senior health workers WHO/FCH/CAH/05.1

# Adjunctive Drugs with Proven Efficacy for Acute Diarrhea

- **ZINC**
  - In areas where the prevalence of zinc deficiency or the prevalence of moderate malnutrition is high, zinc may be beneficial in children aged > six months
    - Meta-analysis: Zinc 10-20 mg/day may shorten the duration of diarrhea by ≈ 10 hrs (MD -10.44 hours, 95% CI -21.13 to 0.25); and probably reduces the number of children whose diarrhea persists until day seven (RR 0.73, 95% CI 0.61 to 0.88) [1]
    - RCT: Zinc 20mg/day for 2 weeks in addition to pivmecillinam reduced duration of illness and median time of disappearance of blood in stools ($p<0.01$) with fewer episodes of diarrhea during the subsequent 6 months $p<0.03$) [2]

1. Lazzerini M, Ronfani L. Oral zinc for treating diarrhoea in children. Cochrane Database of Systematic Reviews 2013;
2. Roy SK et al. Zinc supplementation in the management of shigellosis in malnourished children in Bangladesh. Eur J Clin Nutr 2008 Jul; 62: 849-55

# Unclear Benefit for Bloody Diarrhea

- **Vitamin A**
  - Several trials found no significant effect on the duration or severity of diarrhea (Bhandari 1997; Faruque AS 1999; Henning 1992; Khatun 2001; Grotto 2003)
  - Beneficial role of vitamin A for children with bloody diarrhea secondary to shigellosis remains unresolved (Hossain 1998; Salam 1999)
- **Probiotics**
  - Probiotics may reduce duration and frequency of diarrhea but more research is needed to guide use of particular probiotic regimens in specific patient groups, e.g. bloody diarrhea (Allen SJ et al.. Cochrane Database of Systematic Reviews 2010).

# Drugs which should NOT be given for Bloody Diarrhea

- **Antimotility agents** (Loperamide; Diphenoxylate and atropine [Lomotil])
- **Antisecretory** (Bismuth subsalicylate)
- **Adsorbents** (Attapulgite)

  - Ameliorate intestinal pain but delay clearance of pathogen and increase toxin production
  - Insufficient or no evidence of efficacy
  - Associated with high rates of side effects: lethargy, ileus, respiratory depression, coma
  - May increase development of HUS

WHO. The treatment of diarrhea: a manual for physicians and other senior health workers . 4th ed. 2005

# Public Health Measures to Prevent Transmission

- Provision of clean, safe drinking water
- Effective and sanitary disposal of human and animal waste
- Safe food preparation and food handling practices
- Education in basic personal hygiene (including handwashing) and environmental sanitation

WHO. The treatment of diarrhea: a manual for physicians and other senior health workers. 4th ed. 2005

# Summary

- Intestinal bacterial infections are the most common cause of bloody diarrhea in developing countries, particularly in children < 5 yrs old
- Empiric antibiotic therapy for acute bloody diarrhea should be targeted against Shigella species
- Anti-amebic therapy should be given when: (+) hematophagous trophozoites of E. histolytica are seen; no response after treatment against Shigella
- Antibiotics generally of no proven benefit against *Salmonella, Campylobacter, Yersinia, Shiga toxin producing Escherichia coli*
- Antimicrobial treatment should be based on suspected or identified specific bacterial pathogen
- Treatment includes: Fluid replacement, continued feeding, zinc
- Preventive measures: provision of safe food and water, adherence to hygienic practices, safe food production and preparation, personal hygiene and environmental sanitation

# Thank you

# Vaccines

- **AVAILABLE VACCINES**
  - **Typhoid fever vaccine**
    - Ty21a oral vaccine- cumulative efficacy for 2.5-3yrs = 48%(95% CI 34-58%)
    - Typhoid Vi parenteral vaccine- 3 yr cumulative efficacy = 55% (95%CI 30-70%)

WHO. Weekly Epidem Rec 2008, 83: 49–6.

- **VACCINES UNDER DEVELOPMENT**
  - **Typhoid Conjugate vaccine** (Phase II and III)

Bhutta ZA, Capeding MR et al Lancet Infect Dis 2014; 14:119.

MacLennan. Human Vaccines & Immunotherapeutics 2014;10: 1478–93.

  - **Shigella vaccine** - live-attenuated vaccine strains and inactivated Shigella vaccine candidates, subunit and whole cell (Phase II and III trials).

Ashkenazi S Ther Adv Vaccines 2013; 1:113.

  - **Campylobacter vaccine** – Capsule Polysaccharide Conjugate Vaccine (Phase II trials)

Status of Vaccine Research & Development for Campylobacter Prepared for WHO PD-VAC 2013

# Measures of Proven Efficacy to Prevent Diarrhea in Infants

- Give only breast milk for the first 4-6 months of life
- Avoiding the use of infant feeding bottles
- Improve practices related to the preparation and storage of weaning foods (to minimize microbial contamination and growth);
- Use clean water for drinking
- Handwashing
- Safe disposal of infant diapers

WHO. The treatment of diarrhea: a manual for physicians and other senior health workers. 4th ed. 2005