Clinical cases: Gastrointestinal infections

Prof. Pierre Tattevin
Infectious Diseases & ICU / Antimicrobial Stewardship Committee
Pontchaillou University Hospital, Rennes, France

‘We need evidence on the best way to use (or not) antibiotics, to convince prescribers, and impact on their practices’

Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study

Rachida el Moussaoui, Corianne A J M de Borgie, Peterhans van den Broek, Willem N Hustinx, Paul Bresser, Guido E L van den Berk, Jan-Werner Poley, Bob van den Berg, Frans H Krouwels, Marc J M Bonten, Carla Weenink, Patrick M M Bossuyt, Peter Speelman, Brent C Opmeer, Jan M Prins

Context

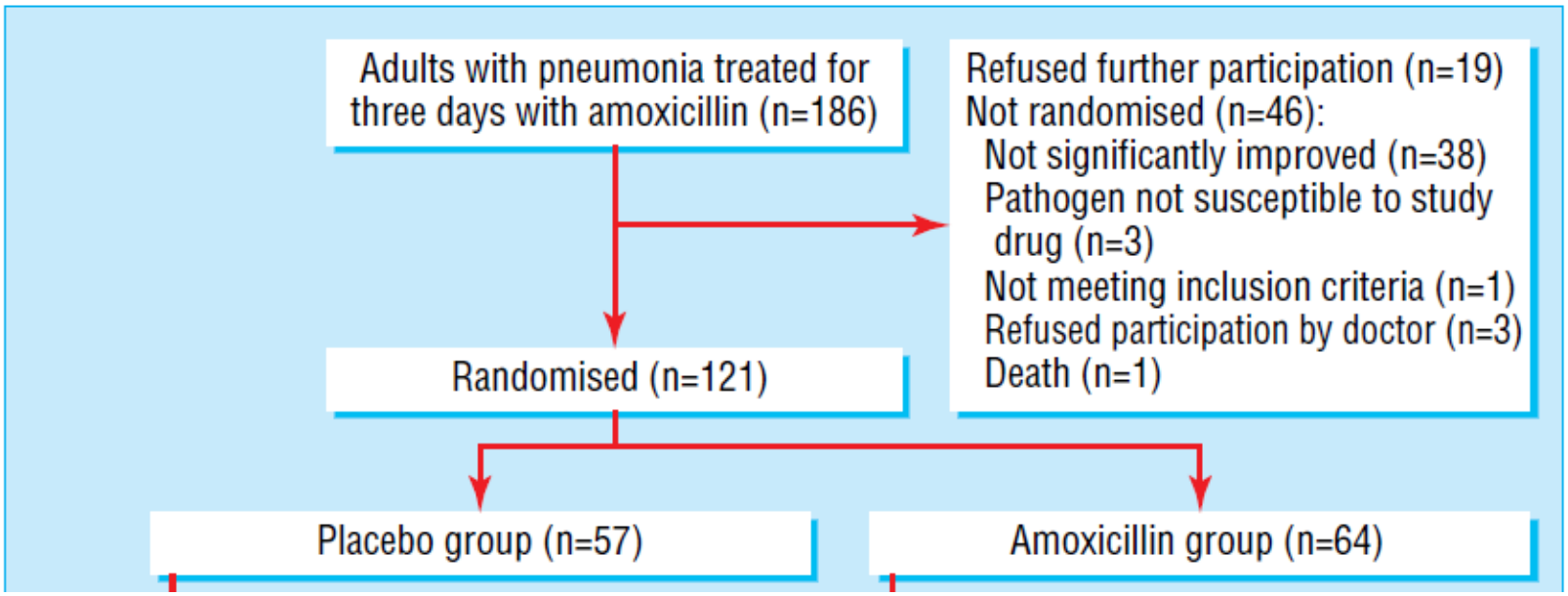
- **The Netherlands, 2000-2003, 9 referral centers**
- **CAP in adults, clinical & radiological, admitted**

Intervention

- **i.v. amoxicillin**
- If patient well at day 3 (i.e. T < 38°C, oral switch feasible)

Randomisation for D3-D8 => **placebo** or oral **amoxicillin**, 750 mg t.i.d.

El Moussaoui R et al. British Med J 2006



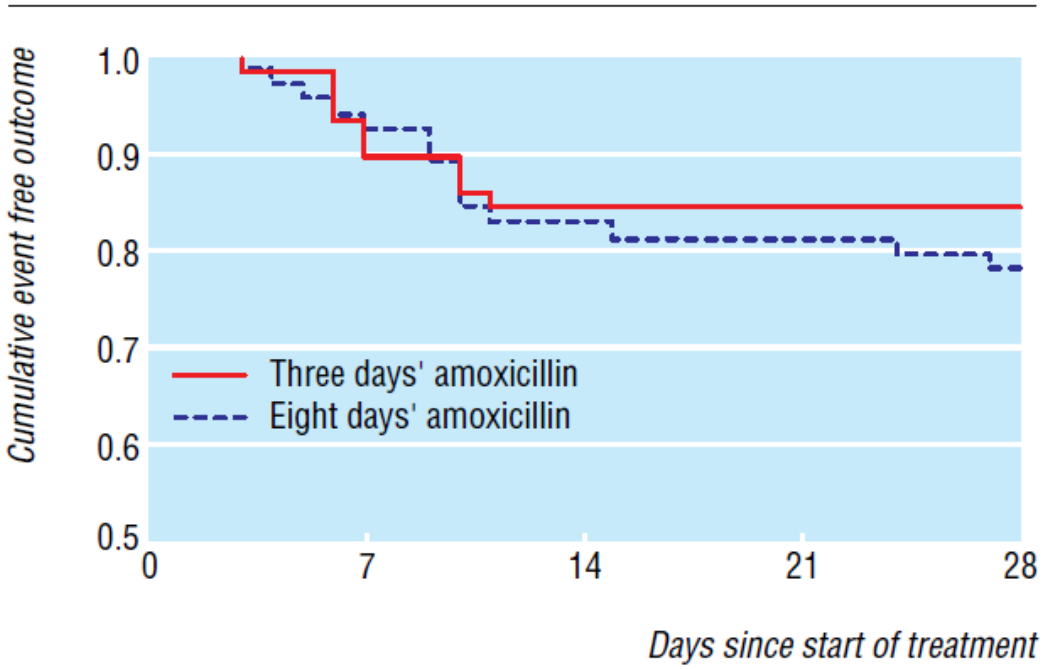
Primary criteria:

Clinical cure, day 10

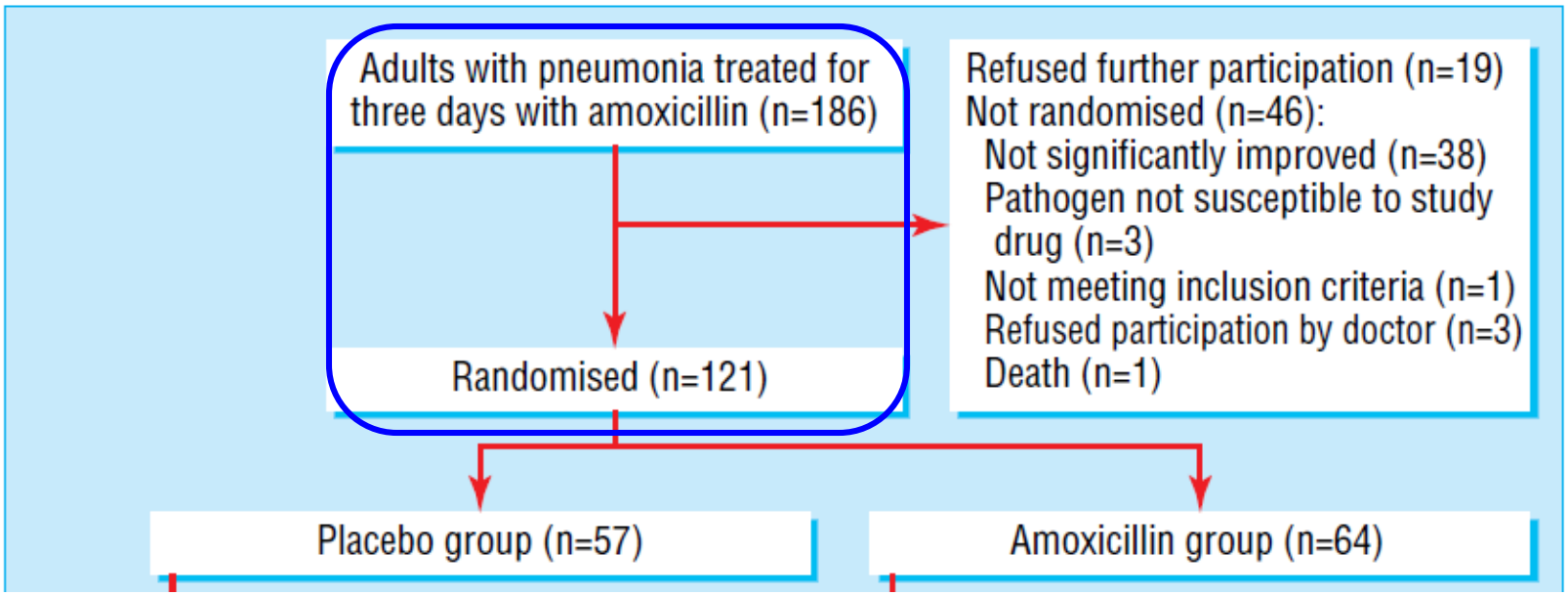
No additional treatment

Non-inferiority proven

Upper 95% CI margin <10%



El Moussaoui R et al. British Med J 2006



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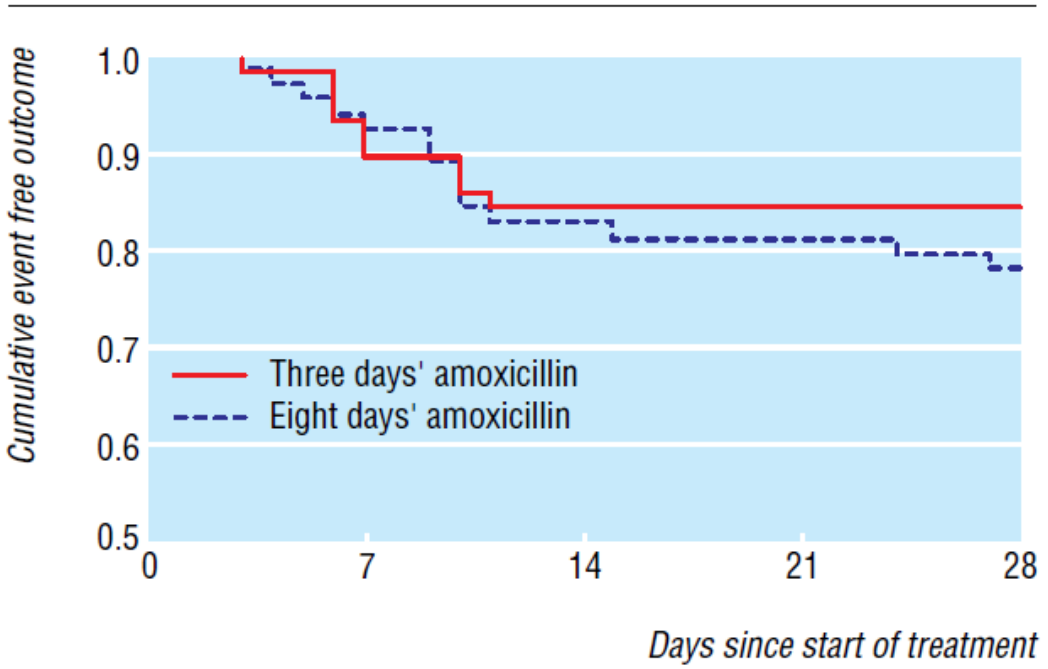
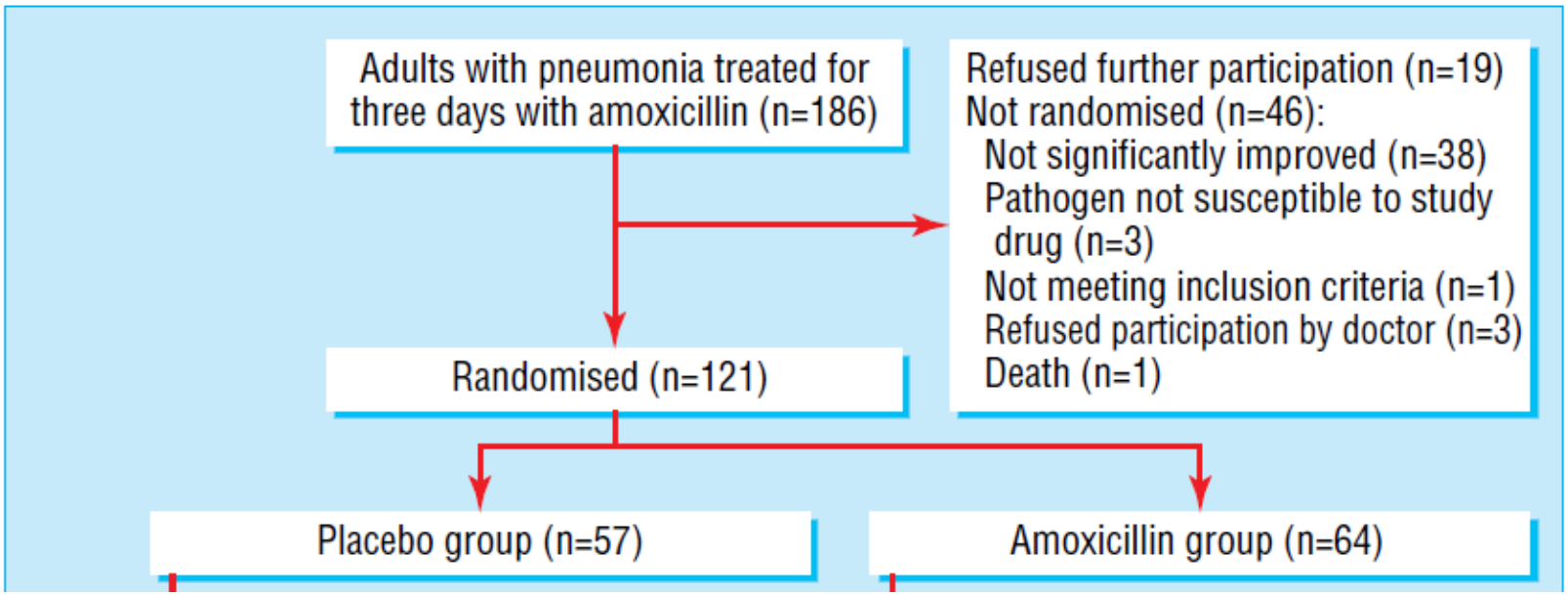


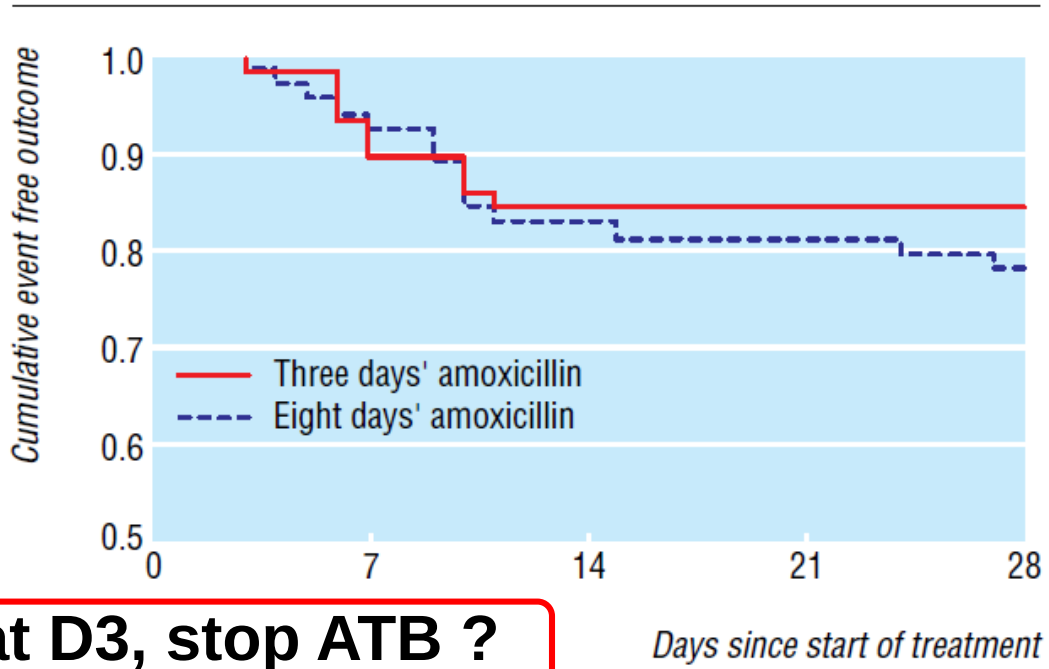
El Moussaoui R et al. British Med J 2006



Primary criteria:

Clinical cure, day 10

No additional treatment



Non-inferiority proven

Upper 95% CI margin <10%

=> when a CAP looks fine at D3, stop ATB ?

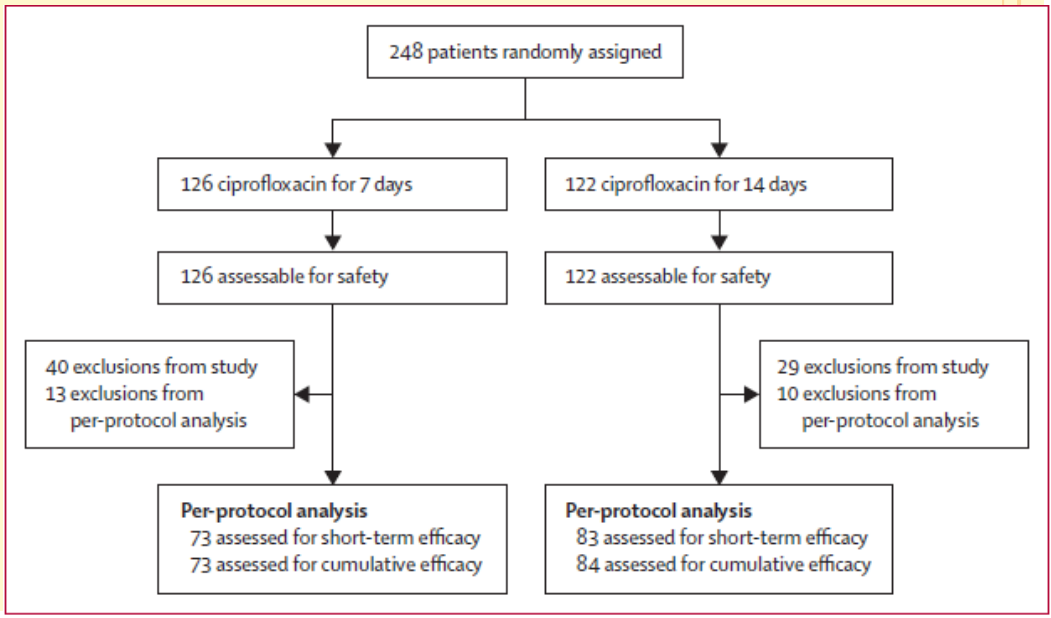
El Moussaoui R et al. British Med J 2006

Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial

Torsten Sandberg, Gunilla Skoog, Anna Bornefalk Hermansson, Gunnar Kahlmeter, Nils Kuylenstierna, Anders Lannergård, Gisela Otto, Bo Settergren, Gunilla Stridh Ekman

Study population

- **Sweden, 21 hosp. (2006-2008)**
- **Non-pregnant women**
- **Outpatient or inpatient**



Intervention

- **Ciprofloxacin 500 mg b.i.d., D1-D7**
- **D8-D15, ciprofloxacin ou placebo**
- **Primary criteria**

= clinical + microbiological cure, 10-14 d post-cipro

Sandberg T et al. Lancet 2011

	Ciprofloxacin for 7 days (n=73)	Ciprofloxacin for 14 days (n=83)
Age (years)	46 (27–62)	41 (23–58)
Recurrent urinary tract infections	11 (15%)	10 (12%)
Complicated urinary tract infections	4 (5%)	10 (12%)
Diabetes mellitus	2 (3%)	7 (8%)
Temperature (°C)	39·2 (38·7–39·7)	39·0 (38·5–39·6)
Flank pain or costovertebral angle tenderness	69 (95%)	79 (95%)
Serum CRP concentrations (mg/L)	100 (56–199)	125 (68–227)
Pyuria	70 (96%)	78 (94%)
Bacteria isolated from pretreatment urine cultures		
Escherichia coli	64 (88%)	79 (95%)
Staphylococcus saprophyticus	3 (4%)	1 (1%)
Klebsiella pneumoniae	3 (4%)	0
Others	3 (4%)	3 (4%)
Positive blood culture	16 (22%)	26 (32%)*
Initial intravenous dose(s) of ciprofloxacin	14 (19%)	11 (13%)

Data are number (%) or median (IQR). All blood cultures grew *Escherichia coli*. *Blood cultures missing for one patient.

Sandberg T et al. Lancet 2011

Ciprofloxacin for 7 days versus 14 days in women with acute pyelonephritis: a randomised, open-label and double-blind, placebo-controlled, non-inferiority trial

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	Ciprofloxacin for 7 days	Ciprofloxacin for 14 days	Difference (90% CI)	Non-inferiority test p value
Short-term efficacy	73	83		
Cure	71 (97%)	80 (96%)	−0·9% (−6·5 to 4·8)	0·004
Clinical failure or recurrent symptomatic urinary tract infections	2 (3%)	3 (4%)	..	
Cumulative efficacy	73	84		
Cure	68 (93%)	78 (93%)	−0·3% (−7·4 to 7·2)	0·015
Clinical failure or recurrent symptomatic urinary tract infections	5 (7%)	6 (7%)	..	

Data are number (%), unless otherwise indicated.

Table 3: Clinical outcomes in the per-protocol population

ORIGINAL ARTICLE

Trial of Short-Course Antimicrobial Therapy for Intraabdominal Infection

R.G. Sawyer, J.A. Claridge, A.B. Nathens, O.D. Rotstein, T.M. Duane, H.L. Evans,

Randomized, multicenter, open-label

- **Complicated intra-abdominal infections**
  + adequate source control

- **Control** = ATB until 2 days without fever, leucocytosis, ileus (max 10 d)
- **Experimental** = fixed duration of ATB, 4 days ± 1

- **Primary outcome** (composite) = SSI, recurrence, or death

Sawyer RG et al. N Engl J Med 2015

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Median duration ATB

- **4 days (IQR 4-5)**
- **8 days (IQR 5-10)**

Sawyer RG et al. N Engl J Med 2015

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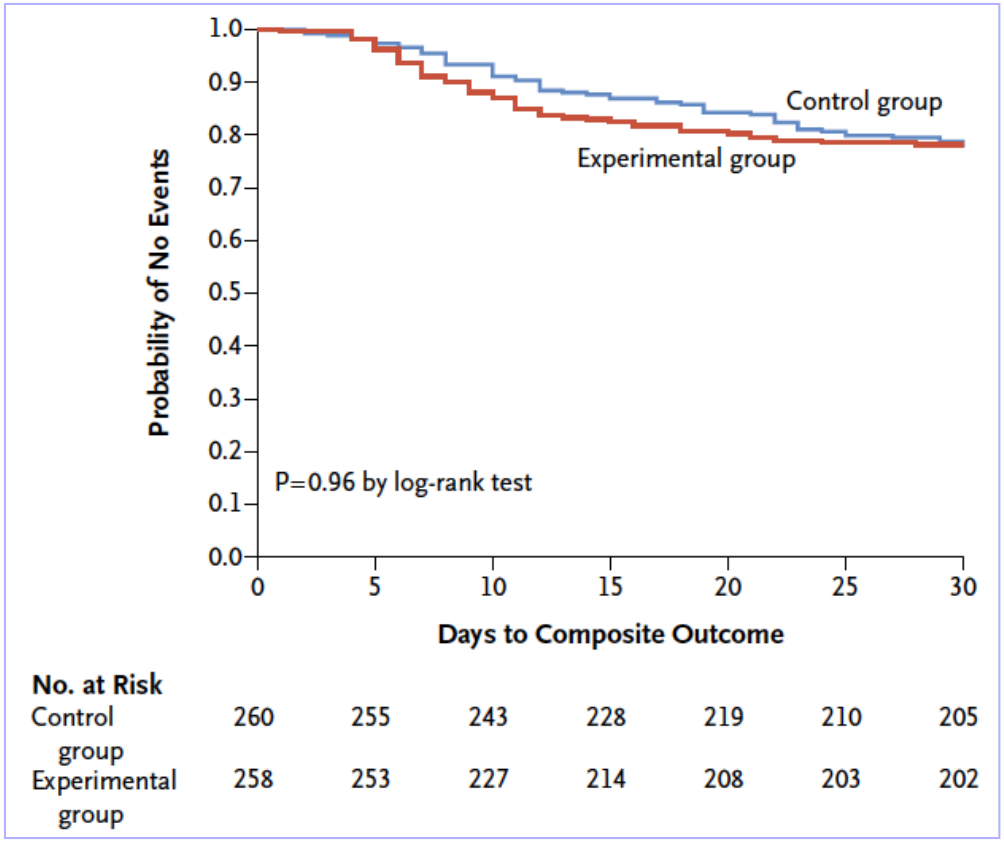

Median duration ATB

- 4 days (IQR 4-5)
- 8 days (IQR 5-10)

Sawyer RG et al. N Engl J Med 2015

Table 1. Estimated Annual Cost Savings in the United States with a Fixed, 4-Day Treatment for Abdominal Sepsis.

Antibiotic	Patients Who Received the Antibiotic	Antibiotic-Days Saved*	Cost Savings†
	percent	*days*	*2015 U.S. $*
Piperacillin–tazobactam	55	660,000	55,367,400
Metronidazole	31	372,000	1,257,360
Ciprofloxacin	27	324,000	1,046,520
Vancomycin	25	300,000	7,200,000
Fluconazole	15	180,000	1,440,000
Ertapenem	10	120,000	30,720,000

* This value is the percentage of patients who received the antibiotic multiplied by 300,000 patients and then multiplied by 4 days.
† Cost savings were calculated as daily charges at Walgreens on April 29,

Wenzel RP et al. N Engl J Med 2015

Case #1

5 year-old boy

- **Acute diarrhea**, 3 days ago, 5 unformed stools/day
- **Moderate fever (38°C)**
- **Well tolerated, although vomitted twice yesterday**
- **Little brother, and older sister, although w/acute diarrhea**
- **PE: vital signs OK, no dehydration**

1. What would you advice ?

a. ORS with instructions

b. anti-diarrheal drugs (loperamide)

c. admission

d. antibiotics

e. stools exam

1. What would you advice ?

a. ORS with instructions

b. anti-diarrheal drugs (loperamide) => may delay cure

c. Admission => no reason

d. Antibiotics => no dysentery, no suspicion of cholera

e. stools exam => very low yield (<5%), no impact

2. What is the most likely diagnosis ?

a. Viral diarrhea

b. Shigellosis

c. Salmonellosis

d. *Clostridium difficile*

e. Giardiasis

2. What is the most likely diagnosis ?

a. <u>Viral diarrhea => gastroenteritis</u>

b. Shigellosis => typically with blood & pain

c. Salmonellosis => less likely to affect siblings simult.

d. *Clostridium difficile* => no recent ATB uptake

e. Giardiasis => chronic diarrhea

Case #1 (continued)

Her mother came back with the boy 3 days later

- ✓ **Diarrhea still active**
- ✓ **Now with blood in stools, & abdominal pain**
- ✓ **Little brother, and older sister, no symptoms anymore**
- ✓ **PE: still vital signs OK, no dehydration (ORS), fever 38.5°C**

1. What would you advice ?

a. ORS with instructions

b. anti-diarrheal drugs (loperamide)

c. admission

d. antibiotics

e. stools exam

1. What would you advice ?

a. ORS with correct instructions

b. anti-diarrheal drugs (loperamide)

c. admission

d. Antibiotics => ciprofloxacin, 3 days

e. stools exam (for surveillance purposes)

What is the yield of stool examination for acute diarrhea in the best labs in 2015 ?

a. <5%

b. 10%

c. 15%

d. 20%

e. 25%

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d. 20%

e. 25%

HL Dupont. N Engl J Med 2009

What is the yield of stool examination for acute diarrhea in the best labs in 2015 ?

Table 7. Clinical characteristics of patients from whose stool selected bacterial pathogens were recovered at 10 hospitals in the United States (n = 30,463 specimens).

	Stool specimens, %			Patients, %		
Pathogen isolated	Total	Visible blood	Occult blood	History of blood in stool	Fever	Abdominal tenderness
Camplyobacter jejuni	2.3	8	52	37	59	45
Salmonella	1.8	5	43	34	72	29
Shigella	1.1	15	59	51	79	34
STEC O157	0.4	63[a]	83	91	35	72
Total	5.6	3		22		

Guerrant RL & al. Clin Infect Dis 2001

What does it change if I prescribe the right ATB, in case his diarrhea is related to ?

a. *Shigella* sp.

b. *Salmonella* sp.

c. Clostridium difficile

d. Shiga-like toxin producing *E. coli* (STEC)

e. *Campylobacter* sp.

f. *Vibrio cholerae*

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f. *Vibrio cholerae*

Good effects:

- Alleviate symptoms
- Shorten duration

=>

- Decrease transmission

What does it change if I prescribe the right ATB, in case his diarrhea is related to ?

a. *Shigella* sp.

b. *Salmonella* sp.

c. Clostridium difficile

d. Shiga-like toxin producing *E. coli* (STEC)

e. *Campylobacter* sp.

f. *Vibrio cholerae*

Potentially bad:

- Chronic carriage (salmonella)
- Risk of HUS (STEC)

=>

- Avoid as much as possible

What is the first-line antibiotic, in 2015, for ?

a. *Shigella* sp.

b. *Salmonella* sp.

c. Clostridium difficile

d. Shiga-like toxin producing *E. coli* (STEC)

e. *Campylobacter* sp.

f. *Vibrio cholerae*

What is the first-line antibiotic, in 2015, for ?

a. *Shigella* sp. => fluoroquinolones

b. *Salmonella* sp. => fluoroquinolones (to be monitored)

c. Clostridium difficile => stop the causal ATB

d. Shiga-like toxin producing *E. coli* (STEC) => azithro

e. *Campylobacter* sp. => macrolide

f. *Vibrio cholerae* => macrolide or doxycyclin

Diarrheal Disease	Treatment in Children	Treatment in Adults
Shigellosis	Azithromycin, 10 mg/kg/day in once-daily dose for 3 days; or ceftriaxone, 50 mg/kg/day given once a day for 3 days	Ciprofloxacin, 750 mg once a day for 3 days; or azithromycin, 500 mg once a day for 3 days
Nontyphoid salmonellosis	None or ceftriaxone, 100 mg/kg/day in two equally divided daily doses for 7–10 days; or azithromycin, 20 mg/kg/day once a day for 7 days	None or levofloxacin, 500 mg (or other fluoroquinolone) once a day for 7–10 days; or azithromycin, 500 mg once a day for 7 days; levofloxacin or azithromycin should be given to immunocompromised patients for 14 days
Enteric, fever including typhoid fever	Ceftriaxone, 100 mg/kg/day in two equally divided daily doses; or azithromycin, 20 mg/kg/day once a day for 7 days	Levofloxacin, 500 mg (or other fluoroquinolone) once a day for 7 days; or azithromycin, 500 mg once a day for 7 days
Campylobacter jejuni diarrhea	Azithromycin, 10 mg/kg/day in a once-daily dose for 3–5 days; or erythromycin, 30 mg/kg/day in 2–4 divided doses for 3–5 days	Azithromycin, 500 mg once a day for 3 days; or erythromycin, 500 mg four times a day for 3 days
Aeromonas species diarrhea	Treat as shigellosis	Treat as shigellosis
Plesiomonas shigelloides diarrhea	Treat as shigellosis	Treat as shigellosis
Cholera (due to *Vibrio cholerae* 01)	Erythromycin, 30 mg/kg/day given thrice daily for 3 days; or azithromycin, 10 mg/kg/day in a once-daily dose for 3 days	Doxycycline, 300 mg in a single dose; or tetracycline, 500 mg four times a day for 3 days; or macrolide (erythromycin, 250 mg thrice daily; or azithromycin, 500 mg once a day) for 3 days

HL Dupont. N Engl J Med 2009

Emergence of Community-Acquired, Multidrug-Resistant Invasive Nontyphoidal *Salmonella* Disease in Rural Western Kenya, 2009–2013

Martina Oneko,[1] Simon Kariuki,[1] Vincent Muturi-Kioi,[1] Kephas Otieno,[1] Vincent O. Otieno,[1] John M. Williamson,[2] Jason Folster,[2] Michele B. Parsons,[2] Laurence Slutsker,[2] Barbara E. Mahon,[2] and Mary J. Hamel[2]

Table 2. Antibiotic Resistance Pattern in Blood Cultures From Participants of Malaria Vaccine Trials in Western Kenya

	Resistant/Tested, No. (%)	
Antibiotic	*Salmonella* B (n = 72)[a]	*Salmonella* D (n = 30)
Ampicillin	64/68 (94.1)	27/30 (90)
Chloramphenicol	54/72 (75)	28/30 (93.3)
Amoxicillin + clavulanate	44/67 (65.7)	13/27 (48.1)
Ceftriaxone	17/72 (23.6)	0/30 (0)
Ciprofloxacin	1/71 (1.4%)	0/30 (0)
Imipenem	0/42 (0)	0/15 (0)

Oneko M & al. Clin Infect Dis 2015

Original Article

Prevalence and antibiotic resistance of bacterial pathogens isolated from childhood diarrhoea in four provinces of Kenya

Willie Kipkemboi Sang[1], Valerie Oundo[2], David Schnabel[2]

[1]*Center for Microbiology Research Laboratory, Kenya Medical Research Institute, 54840-00200, Nairobi, Kenya*
[2]*Enterics laboratory, US Army Research Unit, 606-0621, Nairobi, Kenya*

Sang WK & al. J Infect Dec Ctries 2012

Phenotypic and genetic characterization of *vibrio cholerae* O1 isolated from various regions of Kenya between 2007 and 2010

Njeru Mercy[1], Ahmed Abade Mohamed[2,&], Ng'ang'a Zipporah[3], Goutam Chowdhury[4], Gururaja Perumal Pazhani[4], Thandavarayan Ramamurthy[4], Hamadi I Boga[3], Samuel M Kariuki[5], Oundo Joseph[6]

Mercy N & al. Pan African Med J 2014

Last question

- The boy improves dramatically with cipro, 3 days

- **Stools culture (performed in a lab you don't know):**
  - Predominance of *E. coli*
    - Resistant to ciprofloxacin & trimethoprim/sulfa
    - susceptible to ceftriaxone and imipenem
  - *S. aureus*
  - *C. albicans*

=> What do you do ?

Conclusions

- ✓ Diarrhea is a common disease, most will **resolve with no ATB**

- ✓ **Benefit of antibiotics to be balanced against the risks**
  - ✓ Emergence of resistance may jeopardize future ATB treatment
  - ✓ Gastro-intestinal side effects

=> Restrict ATB use to

- ✓ **Grossly bloody diarrhea**
- ✓ **Cholera-like syndrom**

- ✓ **Currently, stools culture of limited interest for an**

Thank you for your attention !