Inappropriate use of antibiotics within the community

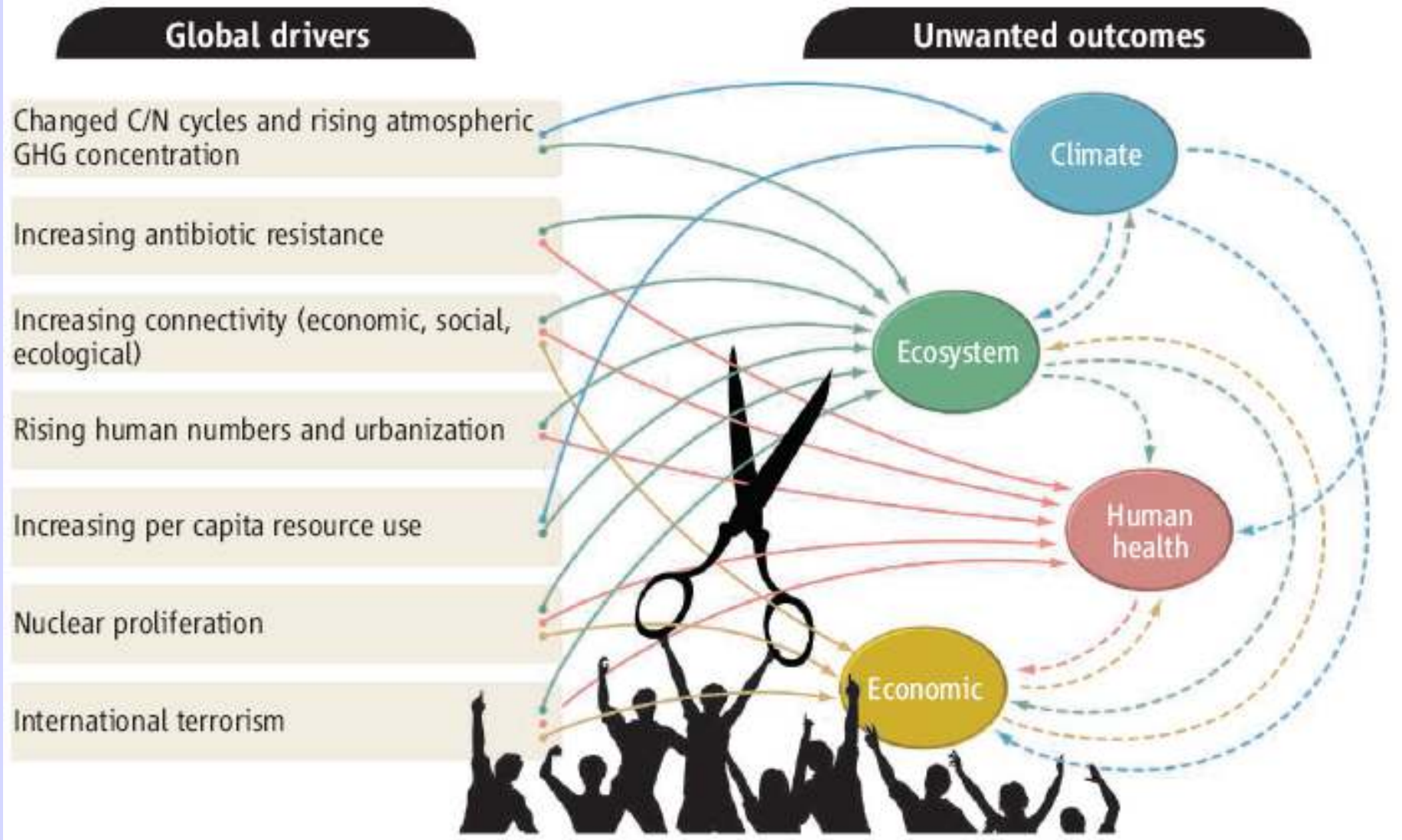
Antimicrobial access and use in enteric infections

Iruka N Okeke

Haverford College
Biology Department

Looming Global-Scale Failures

Walker et al. Science. 2009 Sep 11;325(5946):1345-6.



Interactive effects of global drivers on unwanted outcomes in the state of the world. Some outcomes also act as drivers of others (dashed arrows).

Figure. Itinerant medicine vendor in Oja-tuntun marketplace, Ile-Ife, Nigeria.

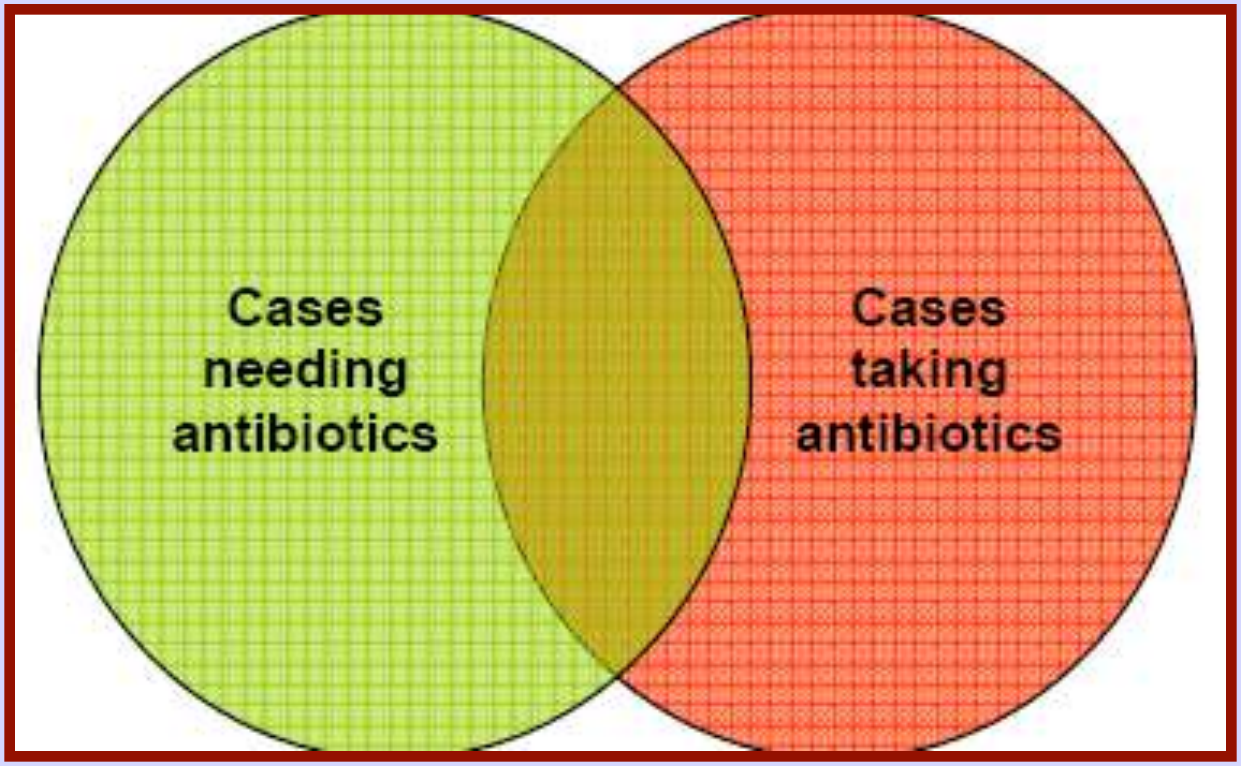
Okeke et al (2007) Emerg Infect Dis, 13 (11) 1640-1646

Frequency of pharmacist recommendation of antimicrobial based on simulated client method surveys

Morgan, DJ, Okeke IN, Laxminarayan R, Perencevich EN, Weisenberg SA (2011) *Lancet Infectious Diseases*. 11 (9) 692 – 701

Country (year)	Cough or runny nose	Pharyngitis (afebrile)	Upper respiratory infection or influenza	Acute sinusitis	Diarrhoea	Urinary tract infection
Americas						
Mexico (1994)[74]	100%*†	..	..	..	..	..
Bolivia (1992)[10]	16%	91%‡	24%	..	92%§	63%
Brazil (2002)[75]	..	..	..	74%	..	..
Europe						
Spain (2007)[76]	..	35%	16%	..	..	80%
Greece (2000)[77]	..	..	..	80%	..	..
Middle East						
Iran (1975)[78]	..	60%	..	..	40%	..
Yemen (1985)[79]	..	..	..	..	9%	..
Africa						
Zimbabwe (2004)[80]	..	..	..	..	9%	8%
Asia						
Sri Lanka (1985)[79]	..	..	..	..	41%	..
Bangladesh (1985)[79]	..	..	..	..	68%	..
Bangladesh (2004)[43]	..	..	..	..	40%	..
Vietnam (1999)[45]	..	..	99%	..	75%	..
Vietnam (1999)[81]	98%	..	..	..	..	..
Nepal (1996)[82]	..	..	..	..	97%	38%
Thailand (1999)[81]	76%	..	..	..	9%	..
Thailand (2006)[83]	..	74%	65%	80%	76%	100%†

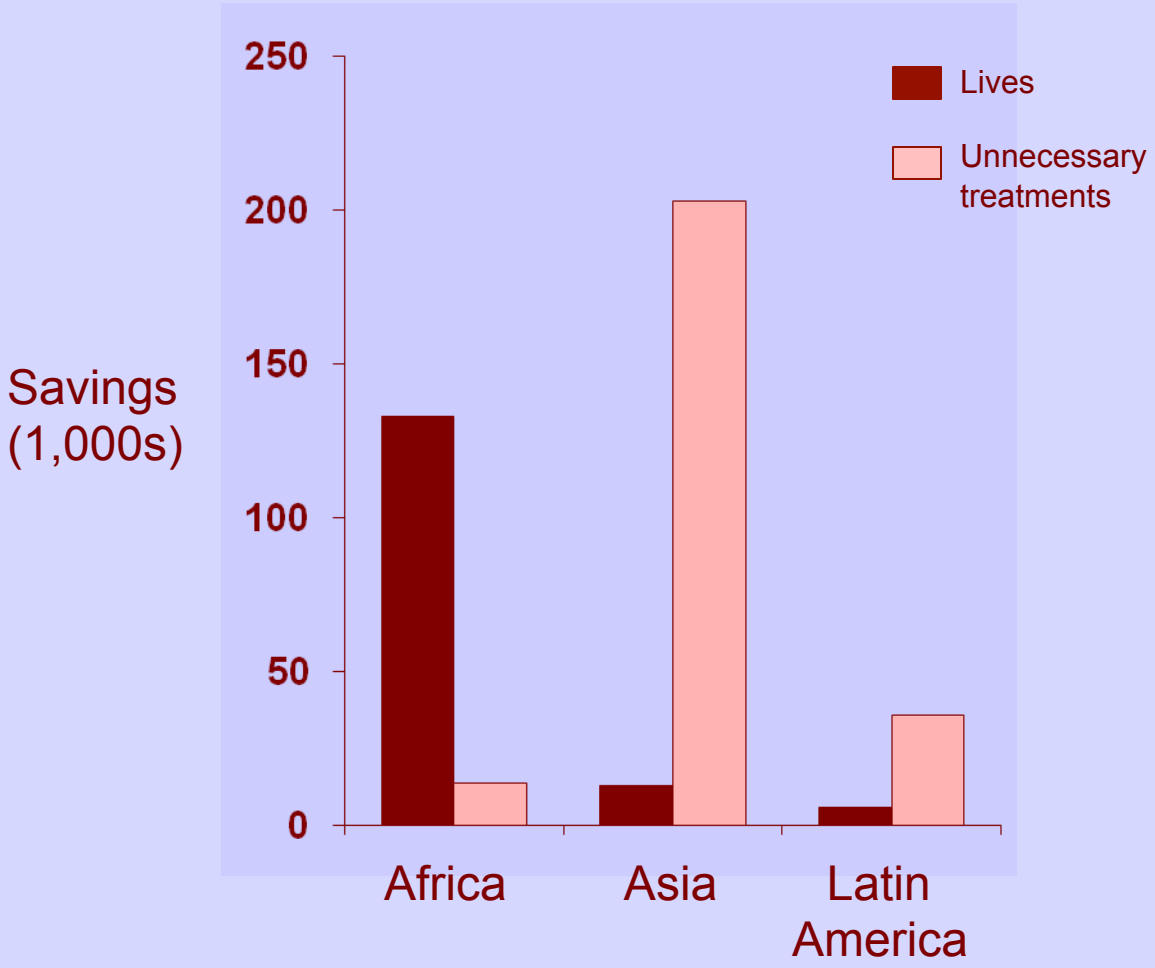
The overlapping relationship b/w patients who need antibiotics and those who take antibiotics.



Källander 2005. Balancing improved access to antibiotics and containment of bacterial resistance. P*aper for discussions at the meeting 'Will we respond to antibiotic resistance in time?' Uppsala Sept 14-17, 2005*
http://soapimg.icecube.snowfall.se/stopresistance/Access.pdf

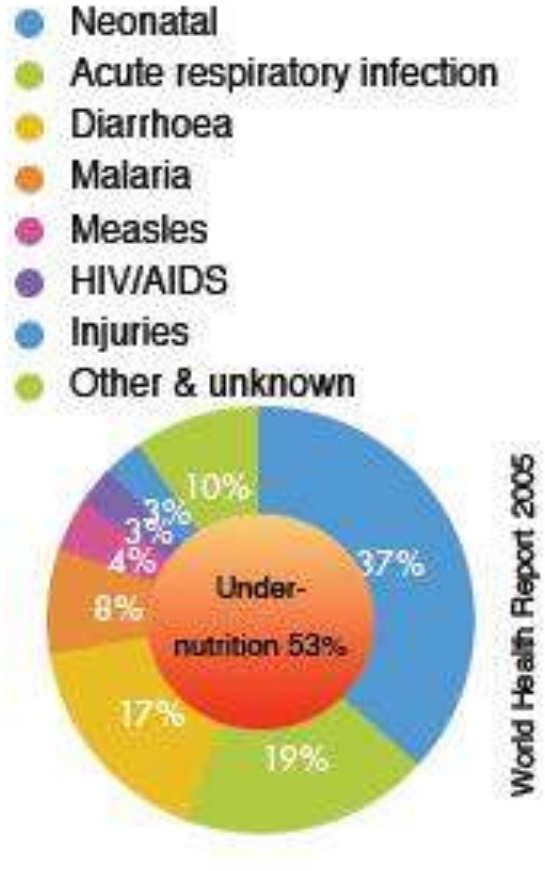
Model-predicted benefits of a new test for pediatric bacterial pneumonia in developing countries

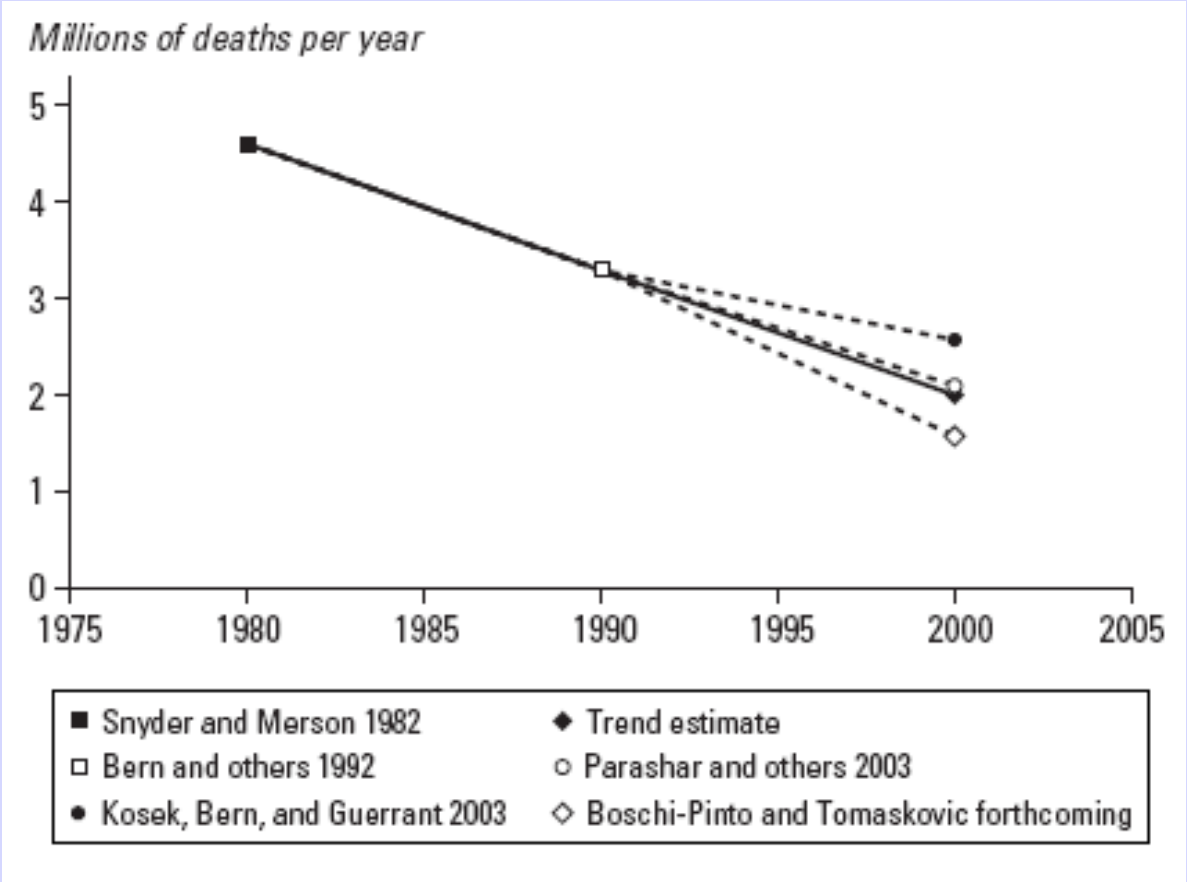
Girosi et al. (2006). Developing and interpreting models to improve diagnostics in developing countries. Nature 444 (Suppl. 1), 3–8.

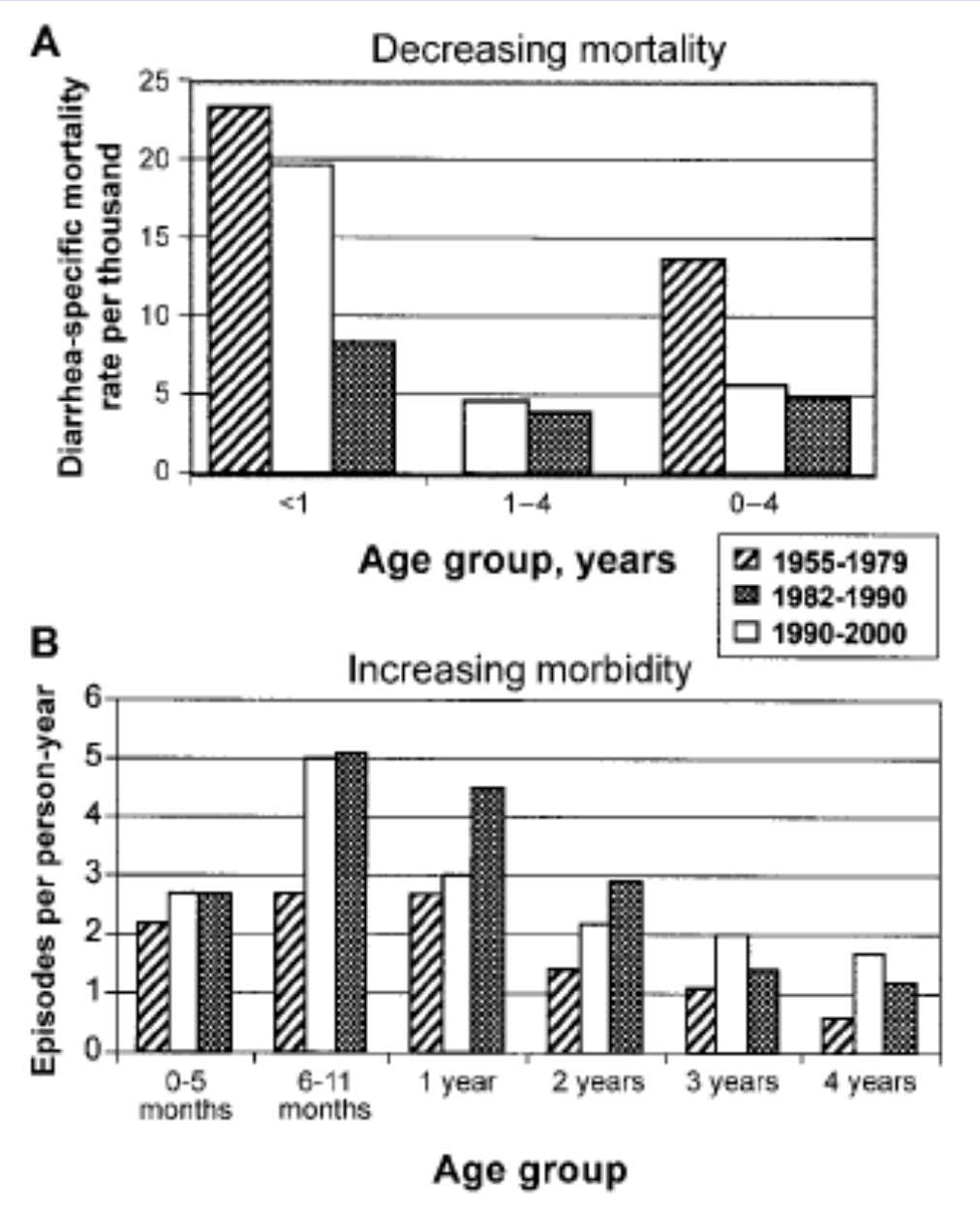


Estimates of diarrheal mortality

(World Health Report 2005,
Disease Control Priorities Project 2nd edition. www.dcp2.org)







Guerrant et al. Clin Infect Dis. 2005 Dec 1;41 Suppl 8:S524-30

Evidence for lasting disability effects resulting from early childhood diarrhea

Guerrant et al. Clin Infect Dis. 2005 Dec 1;41 Suppl 8:S524-30

- Growth shortfalls (~ 8.2 cm by age 7 years)
- Fitness impairment (17% reduced work productivity)
- Cognitive impairment (~10 IQ points)
- School performance (~ 1 year; increased age at starting school and age-for-grade)

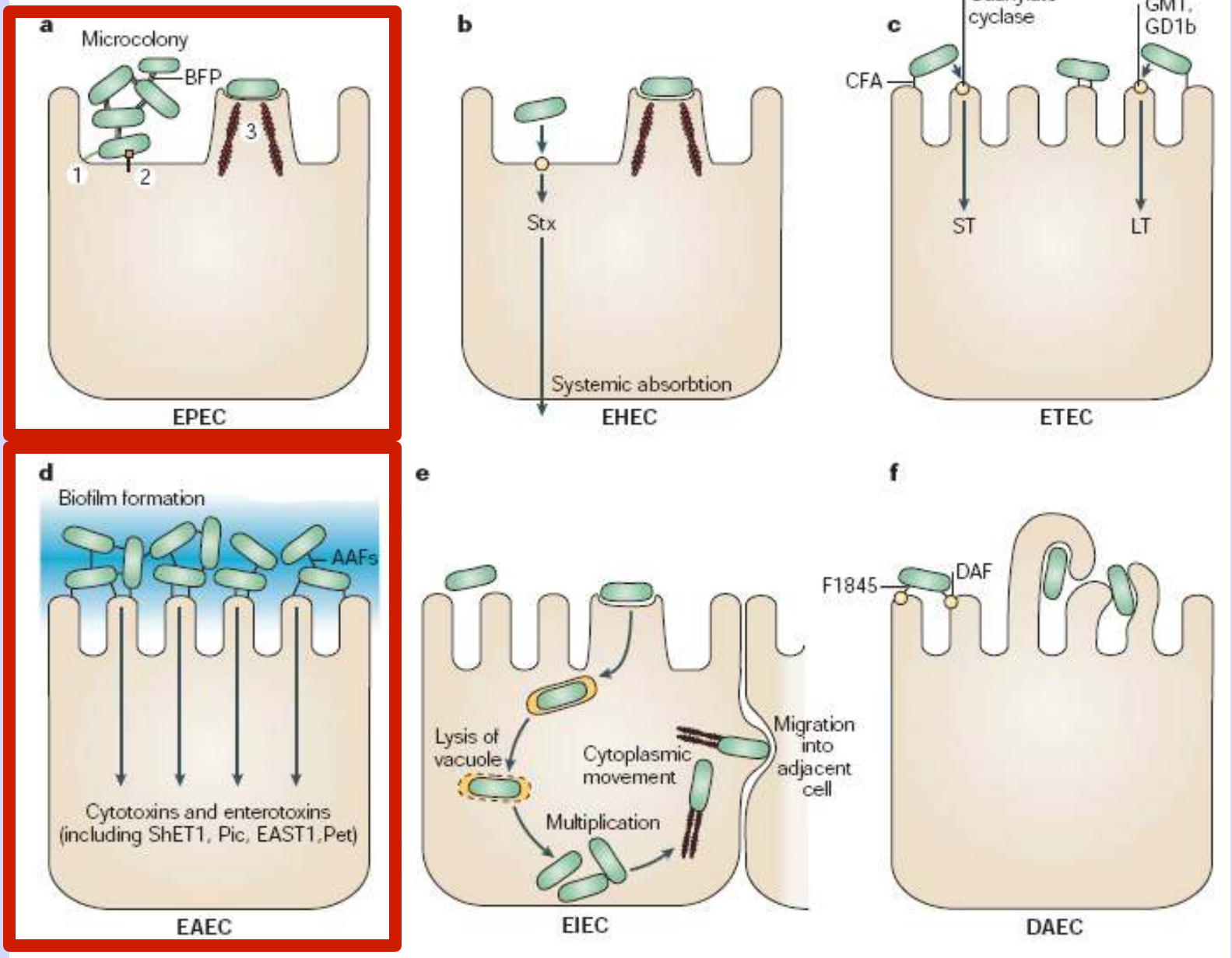
Benefits of understanding the etiology of diarrhea

PREVENTION

- High impact vaccines can be developed
- Agent-specific risk factors (when they exist) can be identified

TREATMENT

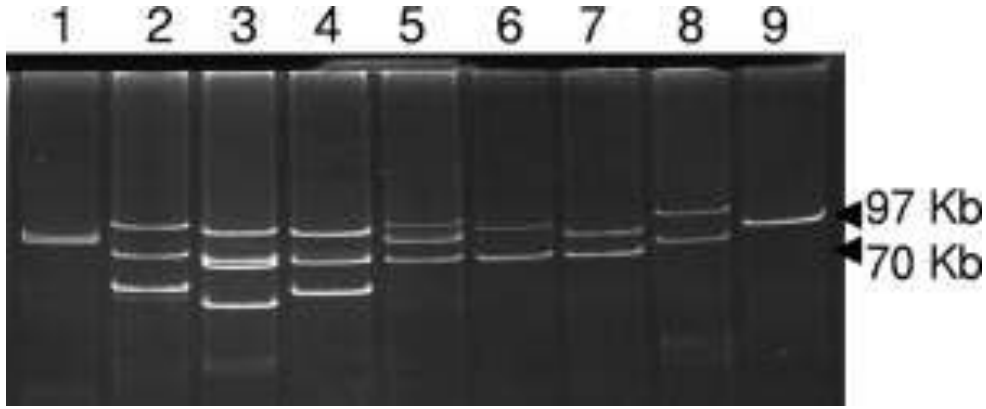
- Strategies for successful empiric treatment can be developed
- Antimicrobials can be conserved for when safe and necessary

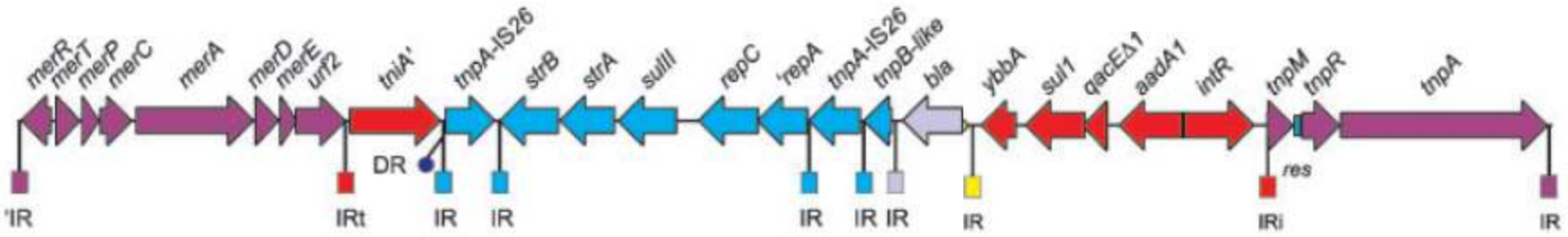


Pathogenic schema of diarrheagenic *E. coli*.

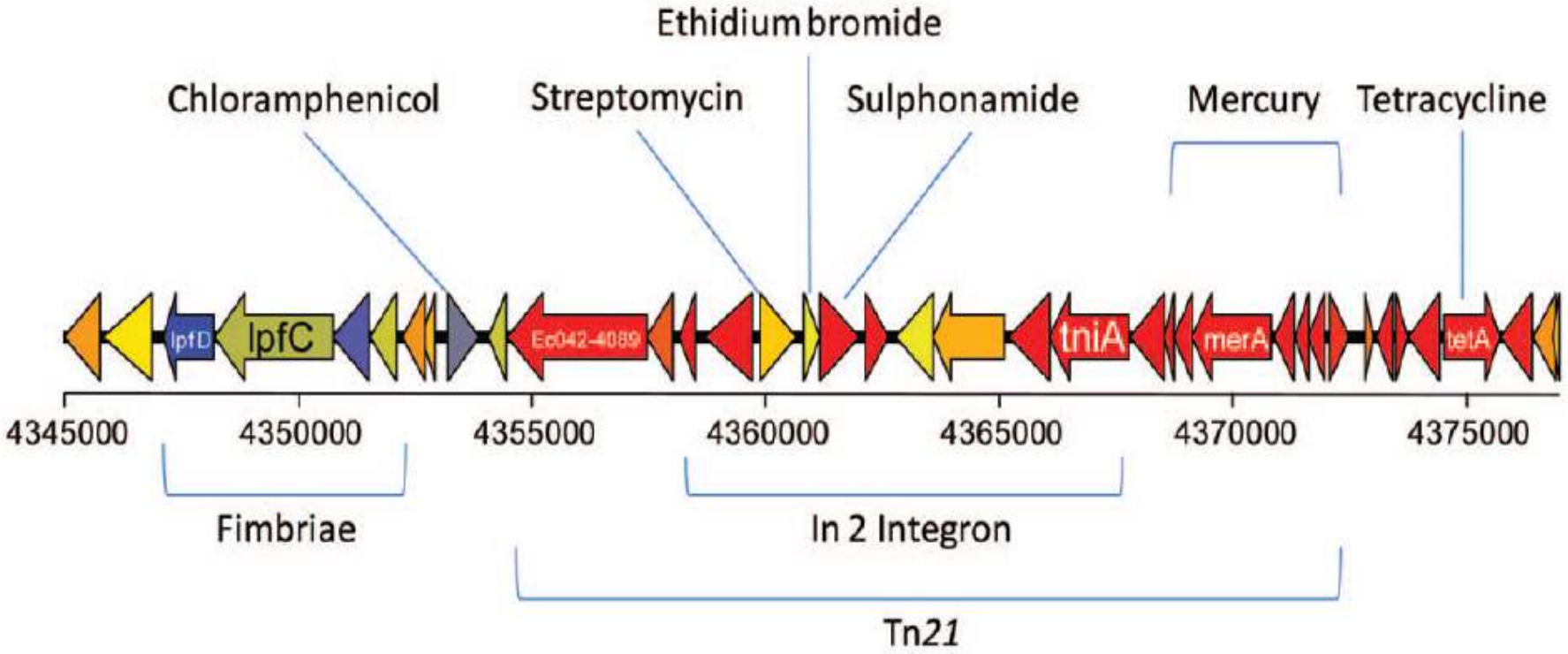
Kaper et al. (2004) Nature Reviews Microbiology, 2, 123-140

Nwaneshiudu, AI, Mucci, T, Pickard, DJ and Okeke, IN (2007) A second large plasmid encodes conjugative transfer and antimicrobial resistance in O119:H2 and some typical O111 enteropathogenic *Escherichia coli. J Bacteriol*, 189: 6074-6079





A resistance island from enteroaggregative *E. coli*



•Chaudhuri RR, *et al.* (2010) *PLoS ONE* 5(1):e8801

•Okeke, IN, Wallace-Gadsden, F, Simons, HR, Matthews, N, Labar, AS, Hwang, J and Wain, J. (2010). *PLoS ONE* 5(11): e14093.

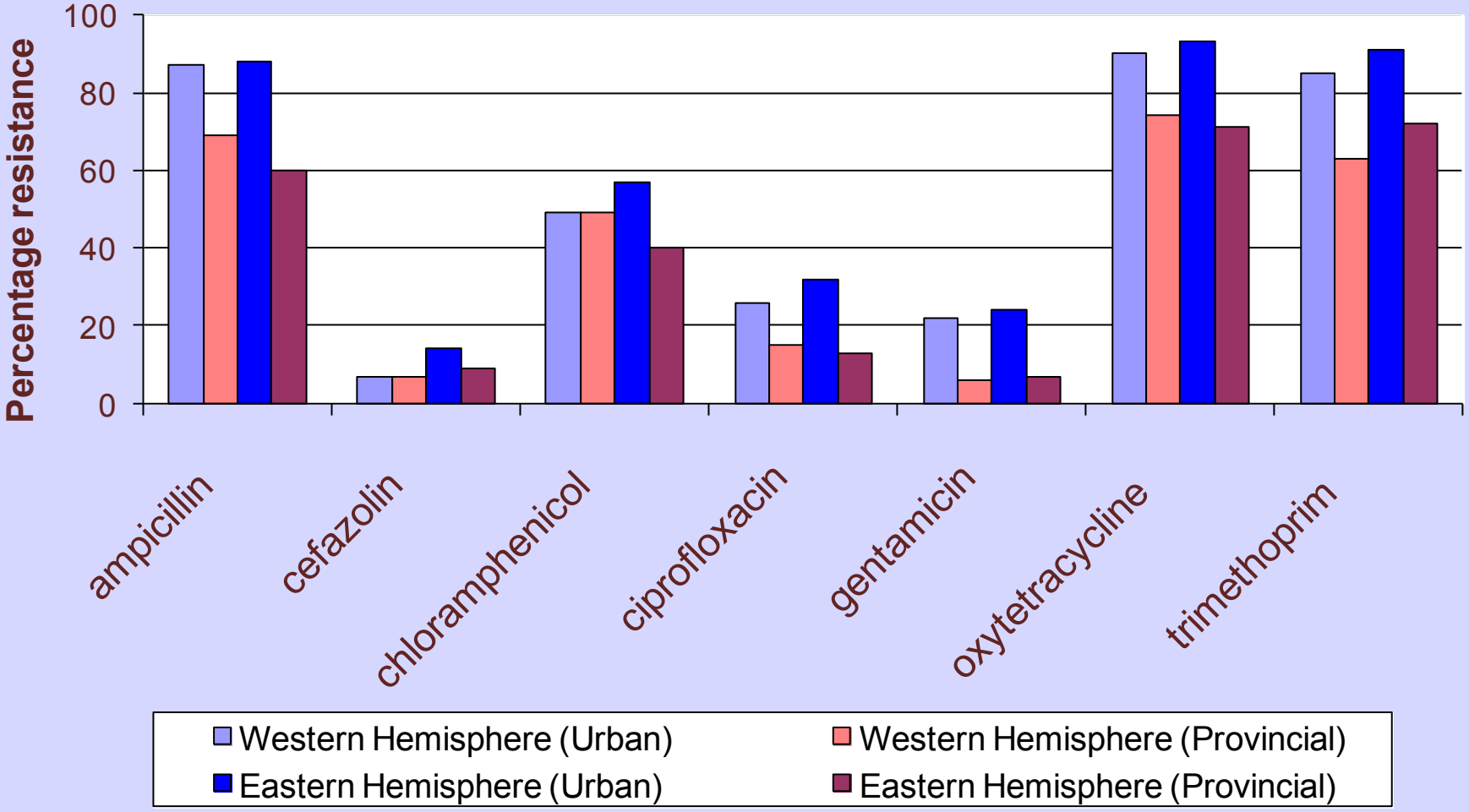
•Wallace-Gadsden, F, Wain, J, Johnson JR and Okeke, IN (2007). *Emerging Infectious Diseases* 13 (5) 757-760.

Antimicrobial use and resistance and the etiology of infantile diarrhea

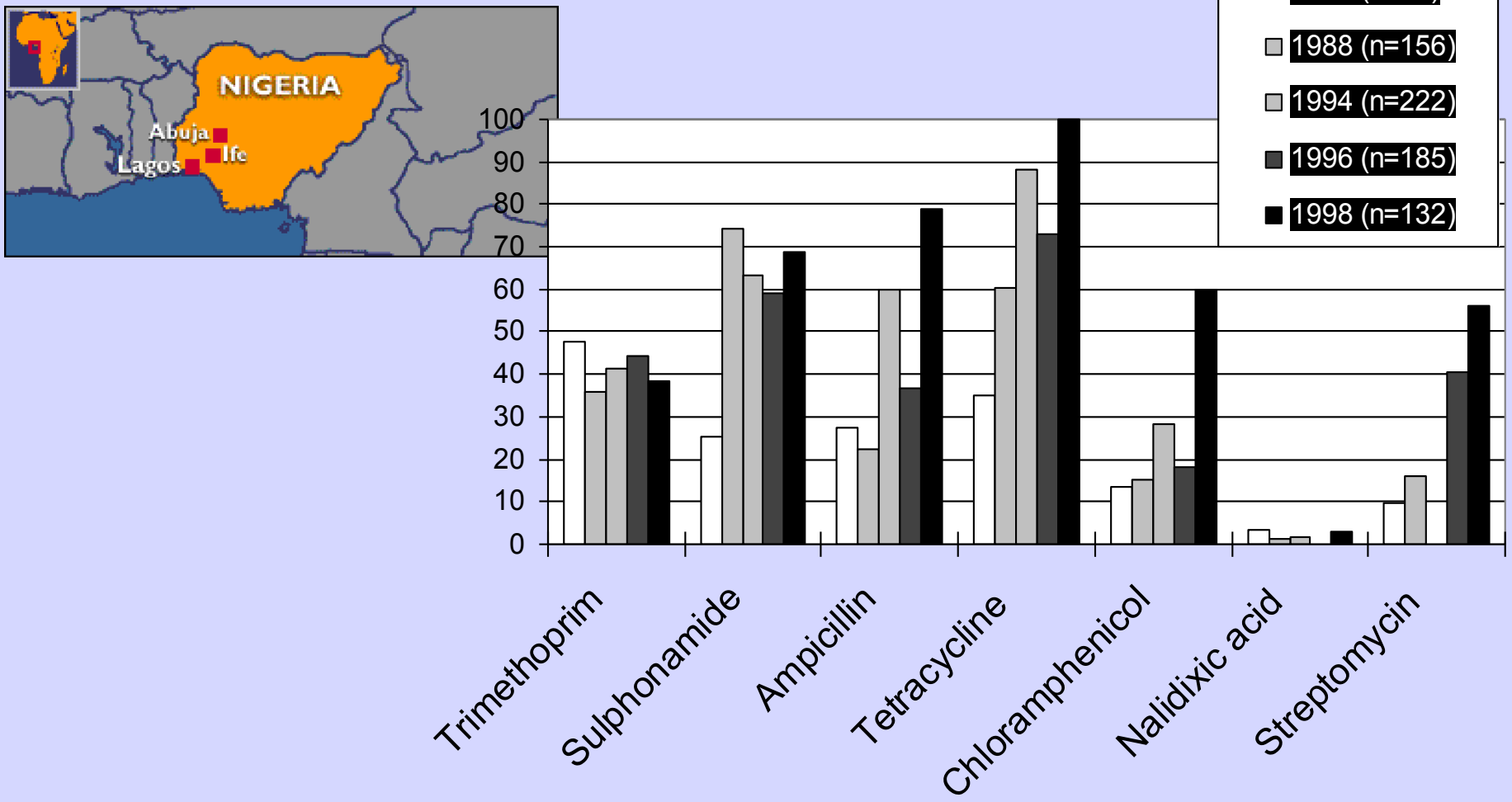
- Antimicrobials are unnecessary in the majority of infantile diarrheas but are too often misused in this condition
- Antimicrobials are needed in bacterial persistent and invasive diarrheas but these cannot be delineated early enough to commence therapy and resistance is a severe problem
- Misuse of antimicrobials more generally impacts resistance in enteric organisms heavily and directly because they readily acquire resistance genes from the fecal flora

Antibiotic resistant fecal *E. coli* from healthy volunteers in 11 developing countries

Nys, S, Okeke, IN, Kariuki, S, Dinant, GJ, Driessen, C, and Stobberingh, EE (2004) *Journal of Antimicrobial Chemotherapy*. 54(5):952-5 .



Percentage of isolates resistant to each agent over time



Okeke, Fayinka and Lamikanra (2000) Emerg Infect Dis, 6, 393

OPEN ACCESS Freely available online PLoS ONE. 2008 Jul 16;3(7):e2727. PLoS one

Antimalarial Therapy Selection for Quinolone Resistance among *Escherichia coli* in the Absence of Quinolone Exposure, in Tropical South America

Ross J. Davidson[1,2], Ian Davis[3,4], Barbara M. Willey[5], Keyro Rizg[2], Shelly Bolotin[4], Vanessa Porter[5], Jane Polsky[6], Nick Daneman[4], Allison McGeer[4,5], Paul Yang[7], Dennis Scolnik[4], Roy Rowsell[3], Olga Imas[5], Michael S. Silverman[3,4]*

1 Queen Elizabeth II Health Sciences Centre, Dalhousie University, Halifax, Canada, 2 Dalhousie University, Halifax, Canada, 3 Lakeridge Health Center, Oshawa, Canada, 4 University of Toronto, Toronto, Canada, 5 Toronto Medical Laboratories/Mount Sinai Hospital Department of Microbiology, Mount Sinai Hospital, Toronto, Canada, 6 St. Michael's Hospital Department of Family & Community Medicine, Toronto, Canada, 7 Ontario Ministry of the Environment, Etobicoke, Canada

Abstract

Background: Bacterial resistance to antibiotics is thought to develop only in the presence of antibiotic pressure. Here we show evidence to suggest that fluoroquinolone resistance in *Escherichia coli* has developed in the absence of fluoroquinolone use.

Methods: Over 4 years, outreach clinic attendees in one moderately remote and five very remote villages in rural Guyana were surveyed for the presence of rectal carriage of ciprofloxacin-resistant Gram-negative bacilli (GNB). Drinking water was tested for the presence of resistant GNB by culture, and the presence of antibacterial agents and chloroquine by HPLC. The development of ciprofloxacin resistance in *E. coli* was examined after serial exposure to chloroquine. Patient and laboratory isolates of *E. coli* resistant to ciprofloxacin were assessed by PCR-sequencing for quinolone-resistance-determining-region (QRDR) mutations.

Results: In the very remote villages, 4.8% of patients carried ciprofloxacin-resistant *E. coli* with QRDR mutations despite no local availability of quinolones. However, there had been extensive local use of chloroquine, with higher prevalence of resistance seen in the villages shortly after a *Plasmodium vivax* epidemic ($p<0.01$). Antibacterial agents were not found in

"…heavy use of chloroquine to treat for malaria likely selected for ciprofloxacin resistance in *E. coli.*"

Antibiotic Resistance: Blame It on Lifesaving Malaria Drug?

Barbara Juncosa

Scientific American July 21, 2008

UNEXPECTED SIDE EFFECTS: Medics in Guyana provide villagers with lifesaving antimalarial drugs that may be contributing to the growing problem of antibiotic resistance in *E. coli.*

John Turnidge… called the study "fascinating," noting that he has long suspected that the overuse of antibiotics was not the only cause of bacterial resistance.

Christopher Plowe …says more study is needed to determine whether health officials should reconsider the widespread use of chloroquine to battle malaria.

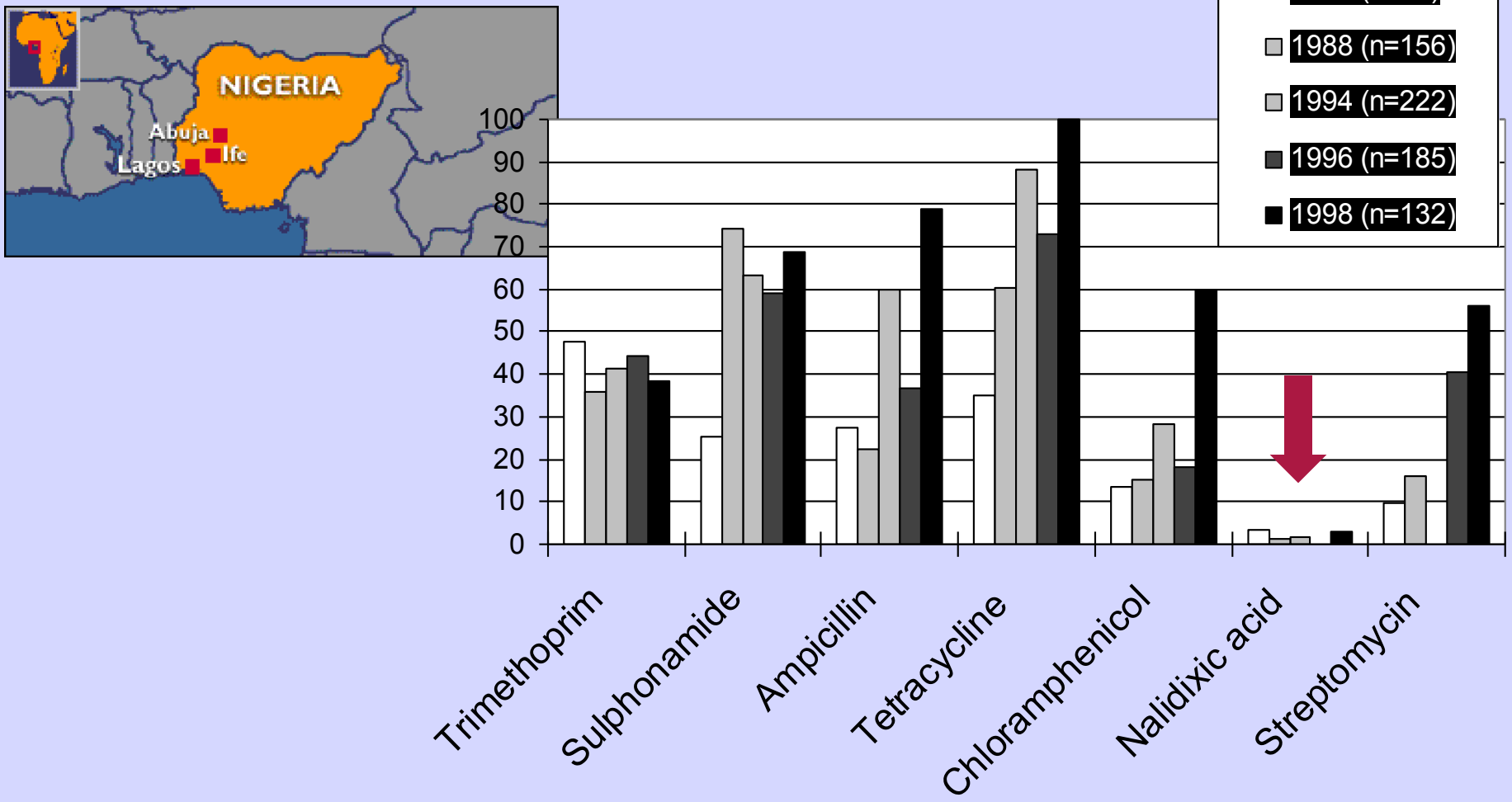
Antimalarial Therapy Selection for Quinolone Resistance among Escherichia coli in the Absence of Quinolone Exposure, in Tropical South America

Where did the putative selection take place?

Posted by ***NJWhite*** on **16 Jul 2008** at **15:54 GMT**

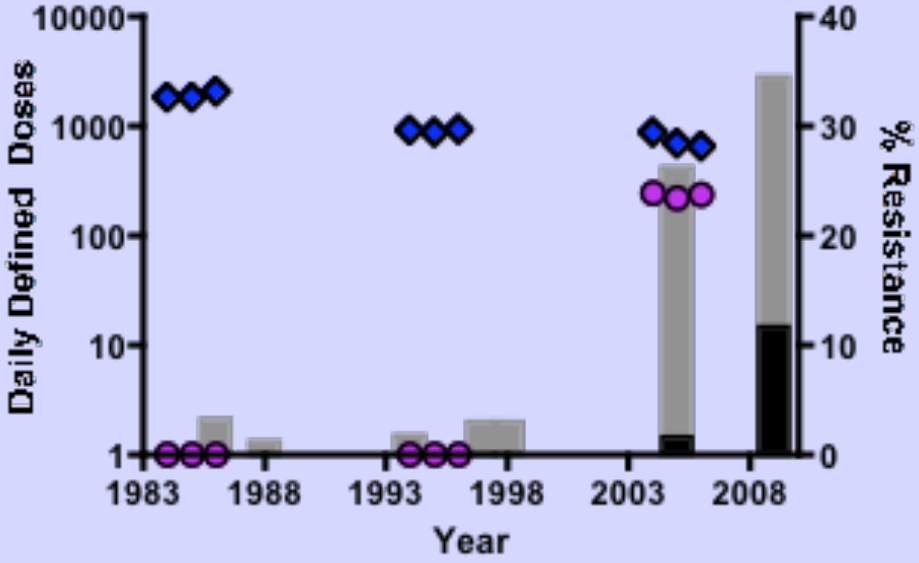
"…If the hypothesis is correct the epidemiological pattern of fluoroquinolone resistance in enteric bacteria (before the introduction of inexpensive fluoroquinolones) should have mirrored that of chloroquine use, with high levels in parts of Africa and Asia."

Percentage of isolates resistant to each agent over time



Okeke, Fayinka and Lamikanra (2000) Emerg Infect Dis, 6, 393

Antimicrobial use and resistance



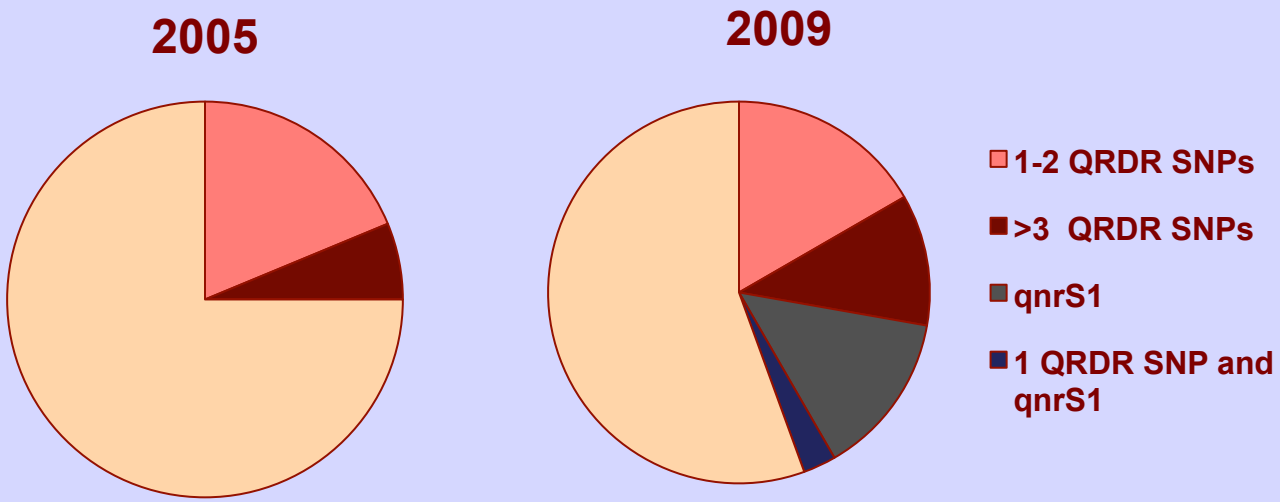
Chloroquine use

Ciprofloxacin use

Low-level quinolone resistance

Fluoroquinolone resistance

Quinolone resistance mechanisms



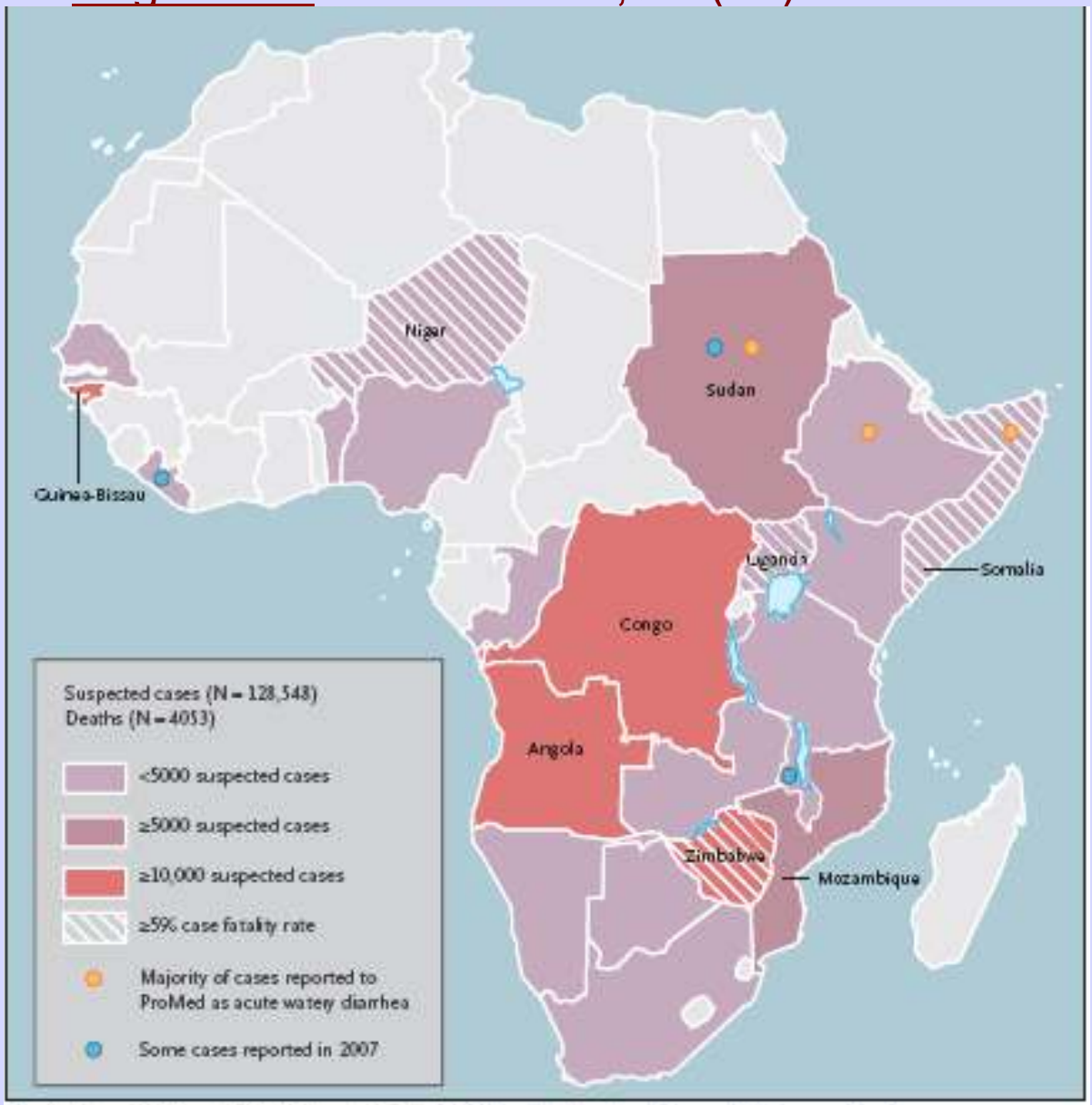
Lamikanra A, Crowe, J, Lijek, RS, , Odetoyin B, Aboderin, AO, Wain, J. and Okeke IN. Unpublished data

Fluoroquinolones come to town

Okeke, Lamikanra et al. Unpublished

NAFDAC Reg No	Product	Weight variation	Friability	Hardness	Disintegra-tion test	Dissolution test
04 3720	Ciprofloxacin HCl USP 500mg	P	0.015	6.72	P	P
04 3221	Ciprofloxacin HCl USP 500mg	P	0.016	10.54	F	P
04 5842	Ciprofloxacin HCl USP 500mg	P	0.096	8.32	P	F
04 4673	Ciprofloxacin HCl USP 500mg	P	0.026	13.54	P	P
04 7405	Ciprofloxacin HCl USP 500mg	P	0.033	10.02	P	F
04 0723	Ciprofloxacin HCl USP 500mg	P	0.013	15.18	P	P
04 5168	Ciprofloxacin HCl USP 500mg	P	0.03	8.28	P	F
04 2170	Ciprofloxacin HCl USP 500mg	P	0.05	8.7	P	F
04 4925	Ciprofloxacin HCl USP 500mg	P	0.153	10.62	P	P
04 4008	Ciprofloxacin HCl USP 500mg	P	0.011	13.16	F	P
04 4061	Ciprofloxacin HCl USP 500mg	P	0.021	too hard to determine	P	P
04 4699	Ciprofloxacin HCl USP 500mg	P	0.012	6.92	P	F
04 5632	Ciprofloxacin HCl USP 500mg	P	0.07	9.7	P	P
04 3002	Ciprofloxacin HCl USP 500mg	P	0.013	14.56	P	P
04 3315	Ciprofloxacin HCl USP 500mg	P	0.029	14.45	P	P

Mintz ED, Guerrant RL.
A lion in our village--the unconscionable tragedy of cholera in Africa. N Engl J Med. 2009 Mar 12;360(11):1060-3.

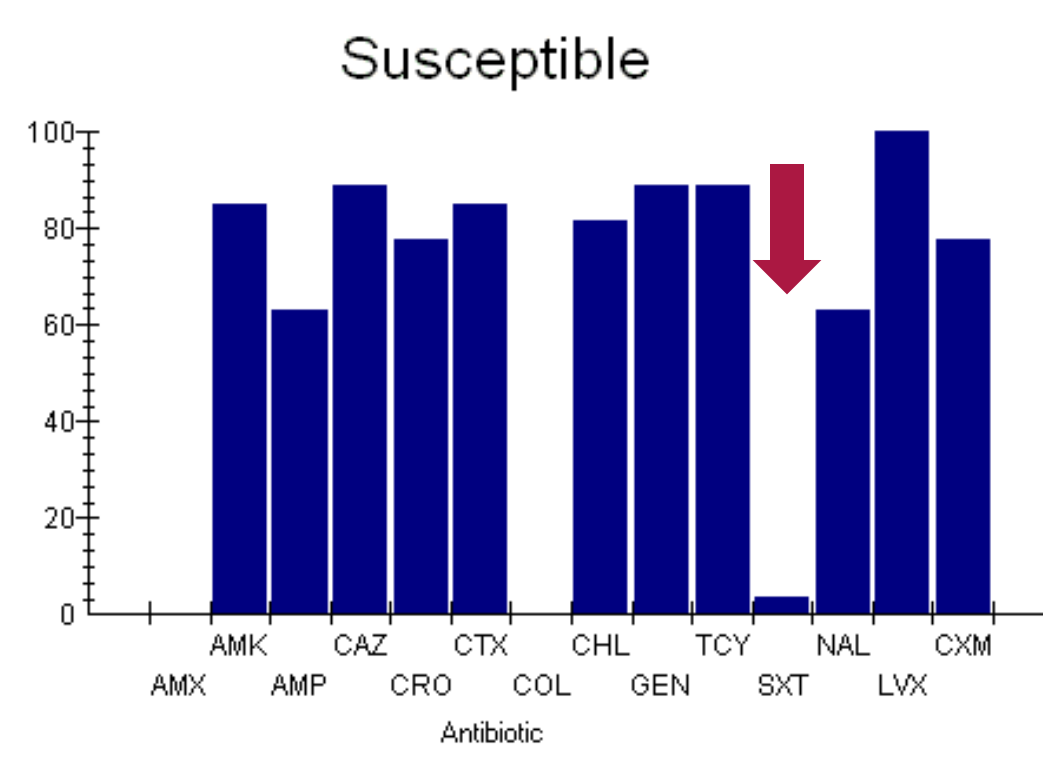


Map of Cholera Outbreaks in Sub-Saharan Africa in 2008, Showing Numbers of Suspected Cases per Country.

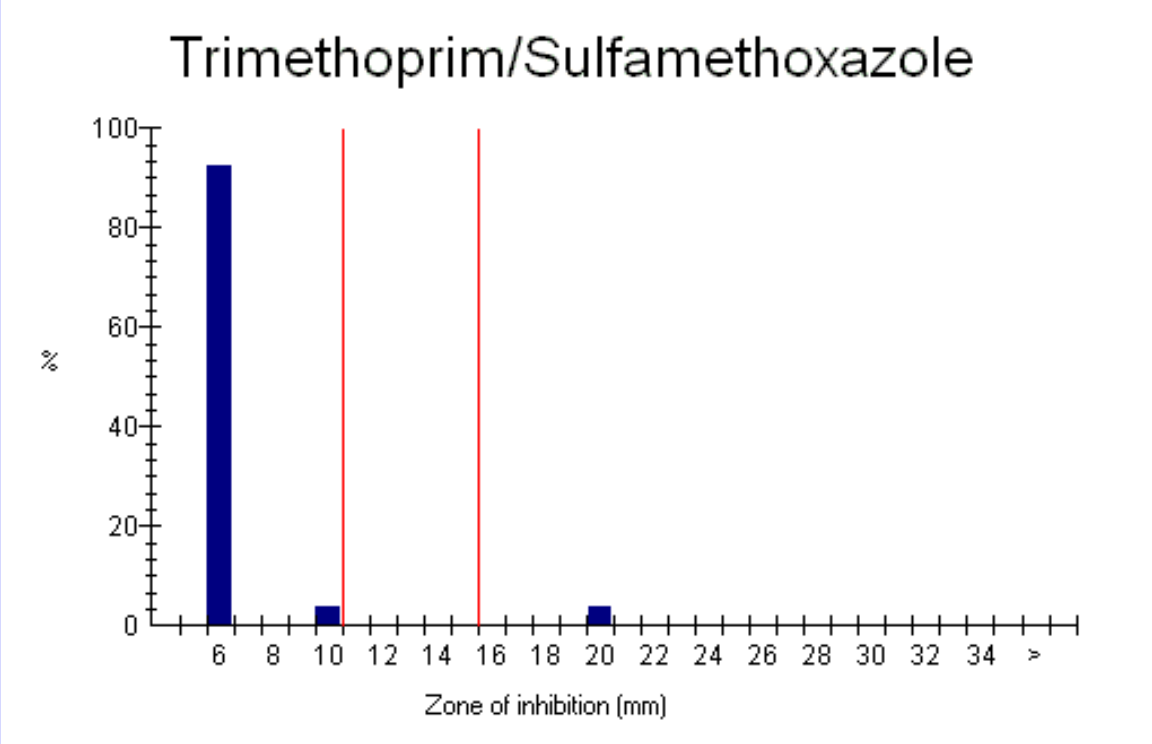
Cholera outbreak (Ghana) Jan 2-June 25, 2006

Opintan, JA, Newman MJ, Nsiah-Poodoh, OA, and Okeke IN (2008). *J Antimicrob Chemother* 62, 929-933.

- 1869 cases and 79 deaths (4.2% case-fatality rate)
- 27 isolates confirmed *V. cholerae* O1 Ogawa by reference lab

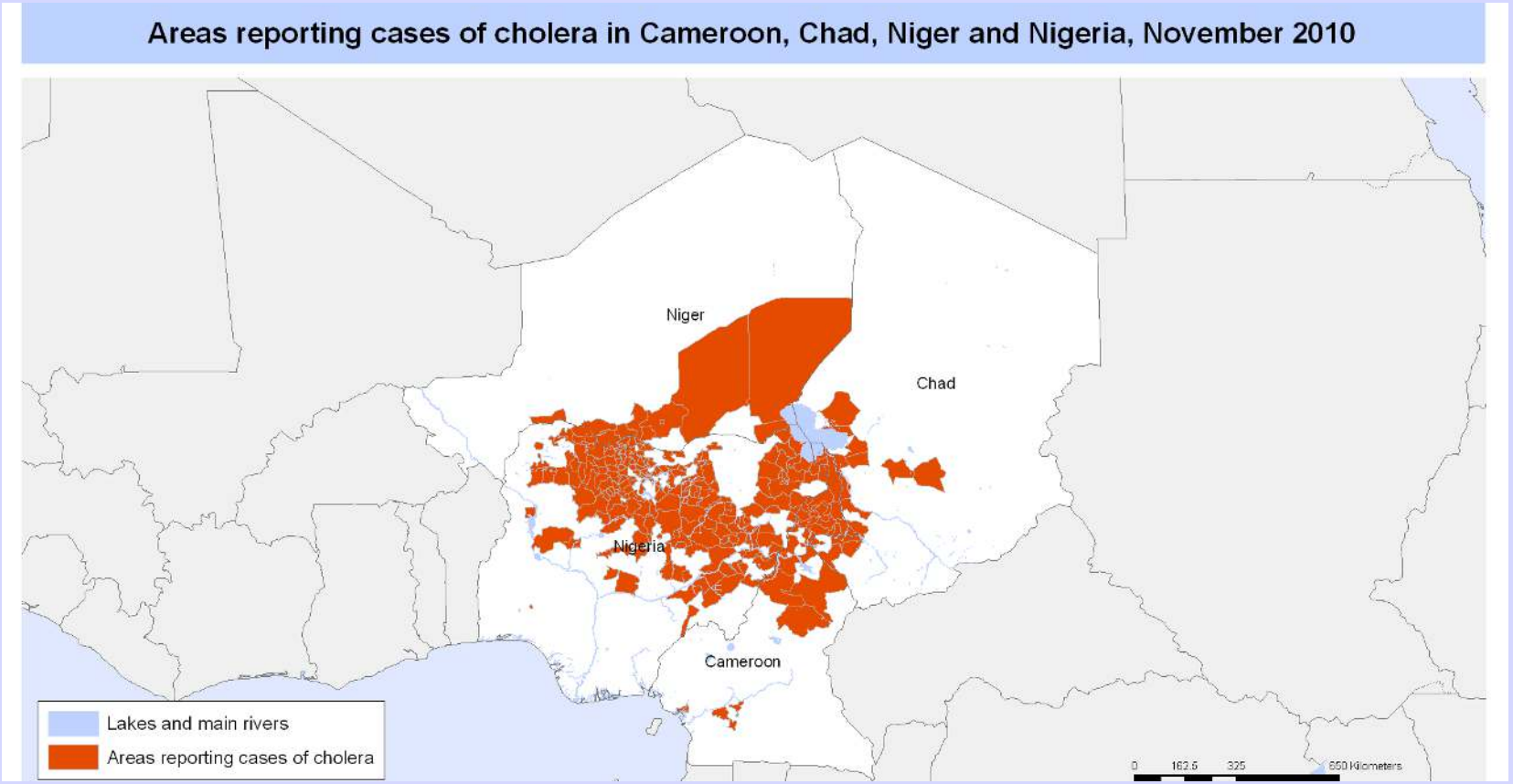


Trimethoprim resistant	26/27
dfrA cassette	19/27
Class 1 integron	0/27
SXT element	23/27
Class 2 integron (*dfrA1-sat-aadA*)	22/27



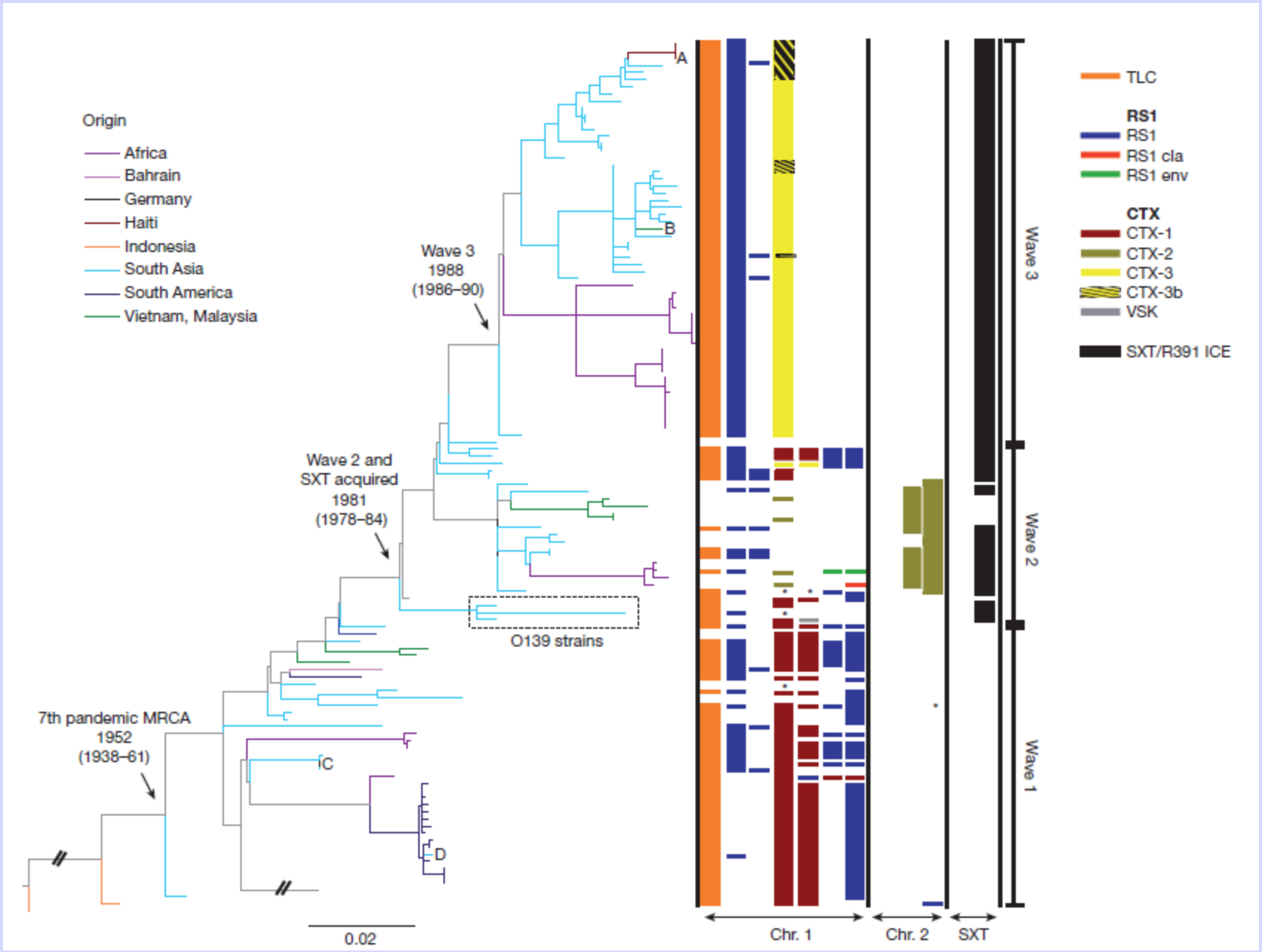
We found multiple elements stably bearing resistant *dfr* genes in most of the *V. cholerae* outbreak isolates

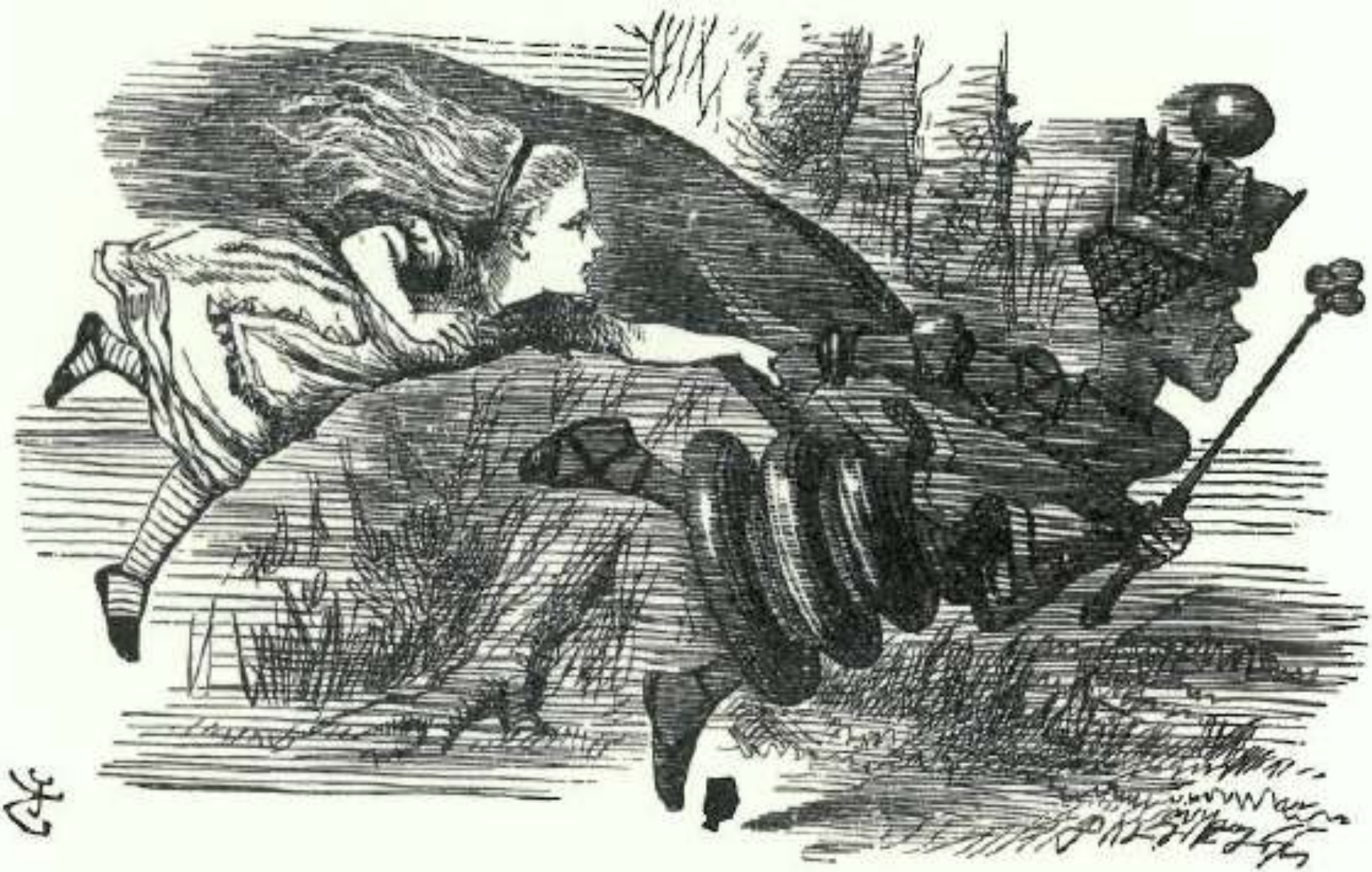
West Africa cholera outbreak 2009-2010



http://www.who.int/csr/don/2010_10_08/en/index.html

Mutreja A, Kim DW, Thomson NR, et al. Evidence for several waves of global transmission in the seventh cholera pandemic. Nature. 2011. doi: 10.1038/nature10392. [Epub ahead of print]





The current cholera conundrum: A Red Queen race

- Antimicrobials are recommended for patients with cholera as a preventive intervention to contain outbreak size.
- Antimicrobials are misused by cholera contacts to ward off the infection
- Resistance to all antimicrobials recommended for cholera treatment has been detected in Africa and Asia
- Cholera isolates possess chromosomal resistance genes and flexible platforms for incorporating new resistances
- Many locales are seeing repeated infections

Recognizing that control of cholera is now entering a new phase with the development of safe, effective and potentially affordable oral cholera vaccines, and that this approach is complementary to, and should not substitute for, the existing effective prevention and control measures that are based on improved access to potable water, sanitation and hygiene,

1. URGES all Member States:

(1) to consider health, hygiene, water, sanitation and environmental issues as integral and interrelated parts of development policies and plans, and accordingly to allocate resources and undertake action, including health and hygiene education and public information in order to prevent the risks of cholera epidemics occurring or to diminish these risks, giving due attention to the situation and needs of population groups most at risk;

(2) to strengthen surveillance and reporting of cholera in accordance with the International Health Regulations (2005), and effectively to integrate surveillance of cholera into overall surveillance systems by building local capacities for data collection and analysis and encompassing information on crucial determinants such as water sources, sanitation coverage, environmental conditions and cultural practices;

(3) to work towards mobilizing sufficient technical and financial resources for coordinated and multisectoral measures for preparation, prevention and control of cholera, as well as other diarrhoeal diseases, in both endemic and epidemic situations, within the framework of health system strengthening and sector-wide approaches, and in the spirit of international solidarity;

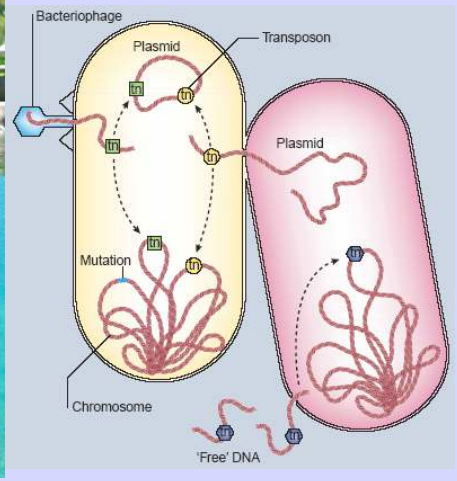
(4) to involve the community and to scale up advocacy measures in view of the intersectoral nature of the disease;

(5) to refrain from imposing on affected or at-risk countries any trade or travel restrictions that cannot be justified on the grounds of public health concerns, in line with Article 43 of the International Health Regulations (2005);

(6) to undertake planning for and give consideration to the administration of vaccines, where appropriate, in conjunction with other recommended prevention and control methods and not as a substitute for such methods;

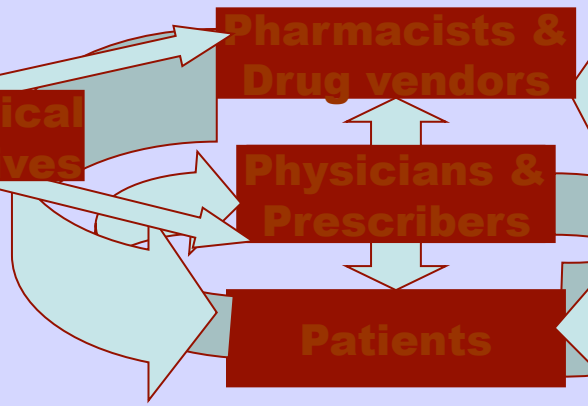
Acknowledgements

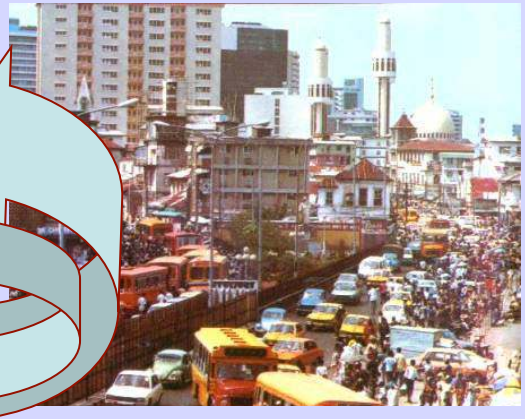
- Society-in-Science: The Branco Weiss Fellowship
- Colleagues and Students at Haverford College
  - Especially Adaobi Nwaneshiudu ‘03, Hannah Simons ‘05, Faith Wallace-Gadsden ‘05, Amy Labar ‘10, Naa Kwarley Quartey ‘11
- Collaborators and hosts at the
  - University of Ghana Medical School, Korle Bu, Accra
    - Japheth Opintan, Mr Nsiah, Mercy Newman
  - Obafemi Awolowo Univ and Teaching Hospitals Complex, Nigeria
    - Diipo Aboderin, Adebayo Lamikanra, Tunde Odetoyin
  - Wellcome Trust Sanger Institute, Cambridge
  - Brazil
    - Isabel Scaletsky, Cristiane Thompson, Ana Carolina Vicente
- CDDEP



[Without diagnosis, there is no rational treatment. Examination comes first, then judgment, and then one can give help]

- Carl Gerhadt, Würsburg, 1873





Cholera in the time of resistance

Goma refugee camp in Zaire (1994) where a diarrheal disease outbreak claimed thousands of lives, after one million people fled fighting in Rwanda.

Tom Stoddart/ Hulton Archive/ Getty Images

What happened?

Siddique, et al. *Lancet* 345 (8946):359-61
Goma, Epidemiology Group. 1995. *The Lancet* 345:339-344.

- July 21-August 13 1994
- Simultaneous cholera and dysentery outbreaks
- 47,233 cholera cases, 2,856 deaths from cholera alone between July 21 and 31,1994
- Worst case-fatality (July 23): 48% Average crude mortality rate was 20-35 per 10,000
- Following the acute epidemic 18-23% of children under 5 were malnourished

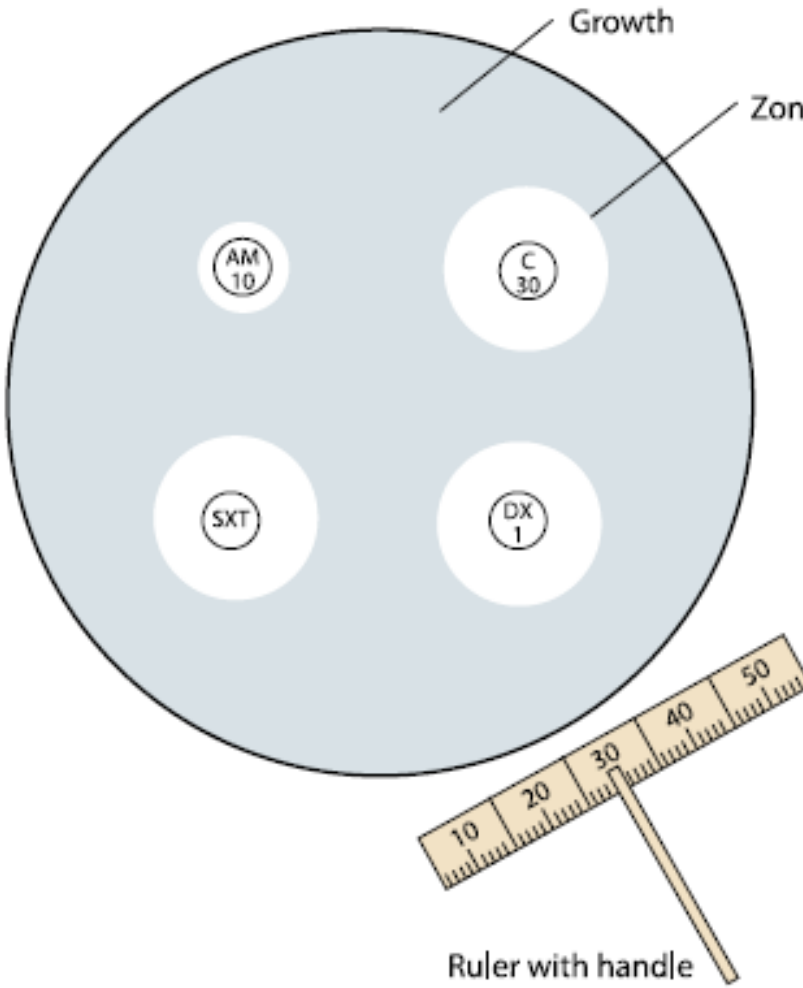
Why did it happen?

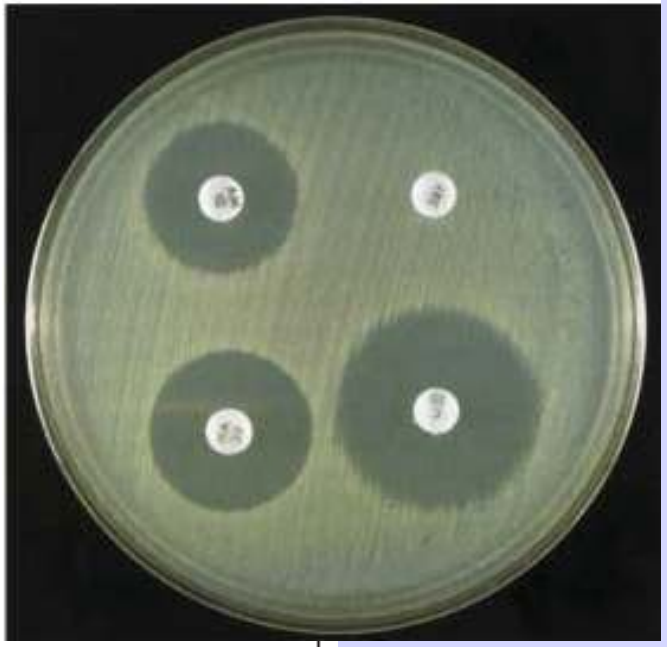
Siddique, et al. *Lancet* 345 (8946):359-61

- Oral rehydration therapy was underutilized
- IV rehydration was too slow – narrow gauge needles in some centers
- Wrong rehydration fluid in some centers

- *Vibrio cholerae* isolates were resistant to tetracyclines, ampicillin, trimethoprim-sulphamethoxazole and nalidixic acid.
- *Shigella dysenteriae* isolates were resistant to nalidixic acid
- Nalidixic acid was used for empiric therapy

FIGURE 6: The antimicrobial susceptibility disk diffusion test: disk placement and measurement of inhibition zone diameters





A ruler on a stick can be used to measure zone inibition diameters if calipers are not available.

http://www.who.int/csr/resources/publications/drugresist/en/IAMRmanual.pdf

“…Before large quantities of drugs are ordered, the sensitivity patterns of local strains of pathogens should be investigated.”

Siddique, A. K., A. Salam, M. S. Islam, K. Akram, R. N. Majumdar, K. Zaman, N. Fronczak, and S. Laston. 1995. Why treatment centres failed to prevent cholera deaths among Rwandan refugees in Goma, Zaire. *Lancet* 345 (8946): 359-61.

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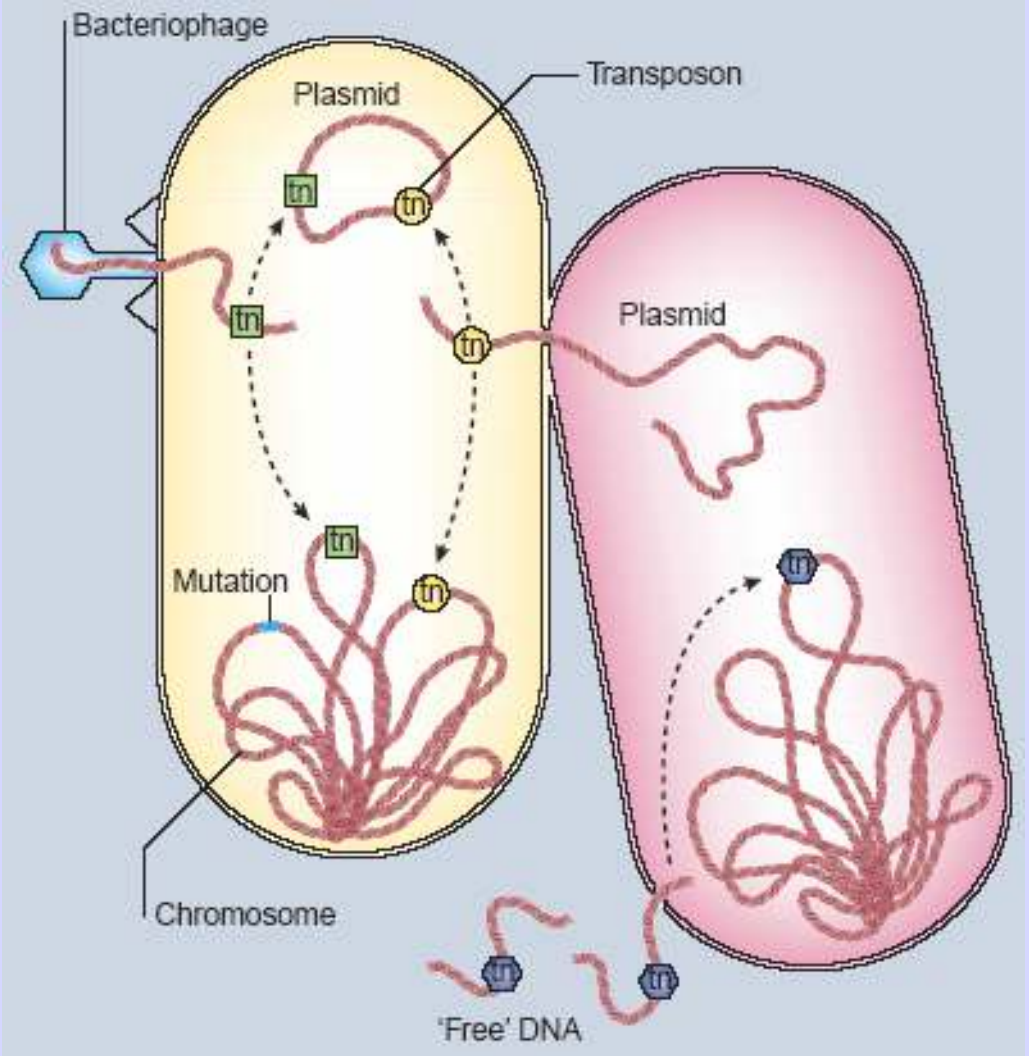
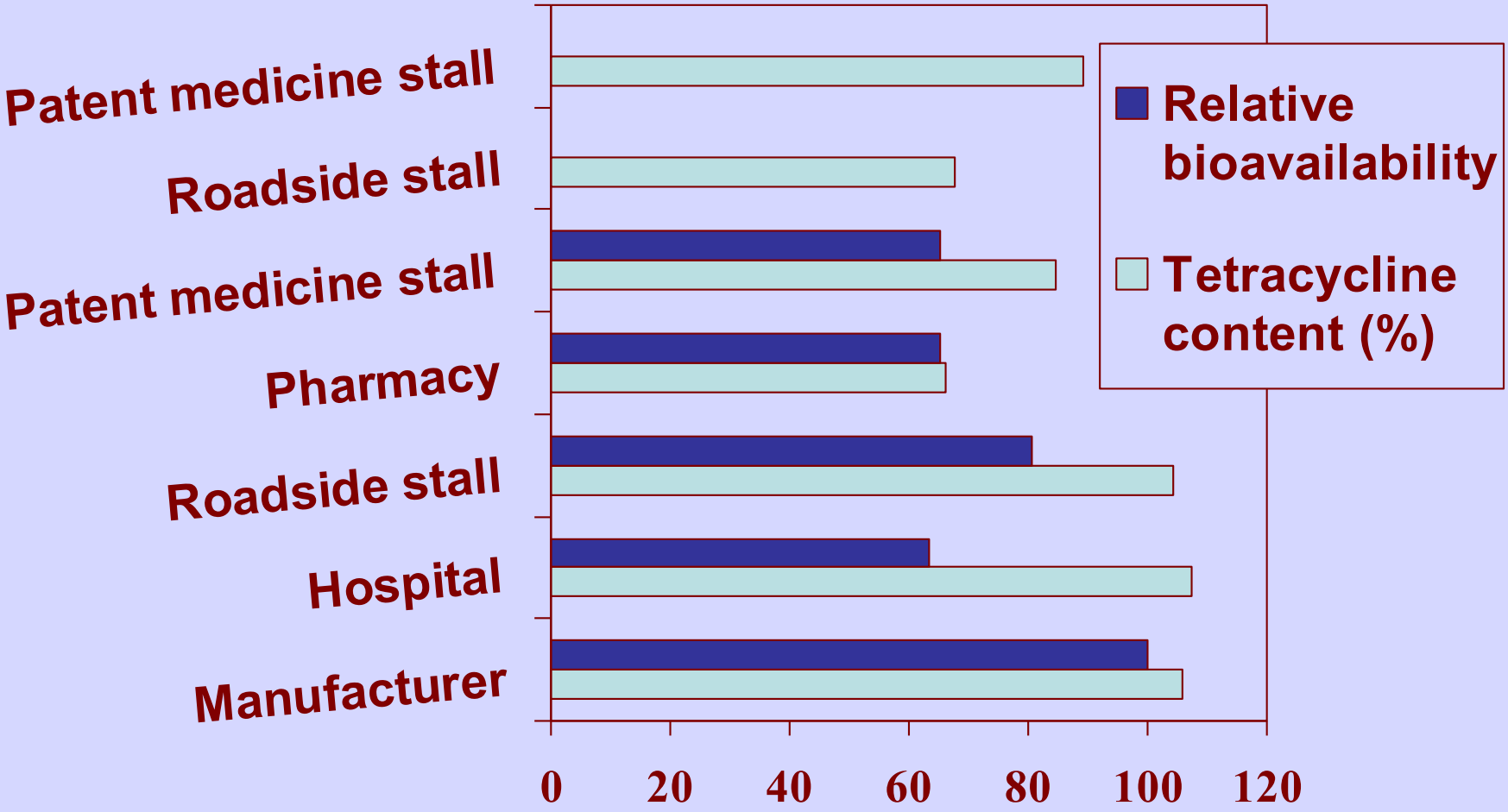
Levy & Marshall Nat Med. 2004 Dec;10(12 Suppl):S122-9.



Tetracycline content and relative bioavailability from dispensed capsules



Okeke and Lamikanra (1995) Int J.Antimicrob Ag 5, 245.
Okeke et al (1999) Emerg Infect Dis 5, 18