THE IMPACT OF SUB-STANDARD ANTIBIOTICS, IS IT BEYOND THE INDIVIDUAL?

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Agenda

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- Generic drugs- anti-infectives
- Specific examples of antibiotic issues
- Potential globally crises

Clinical Development Program for New Agents

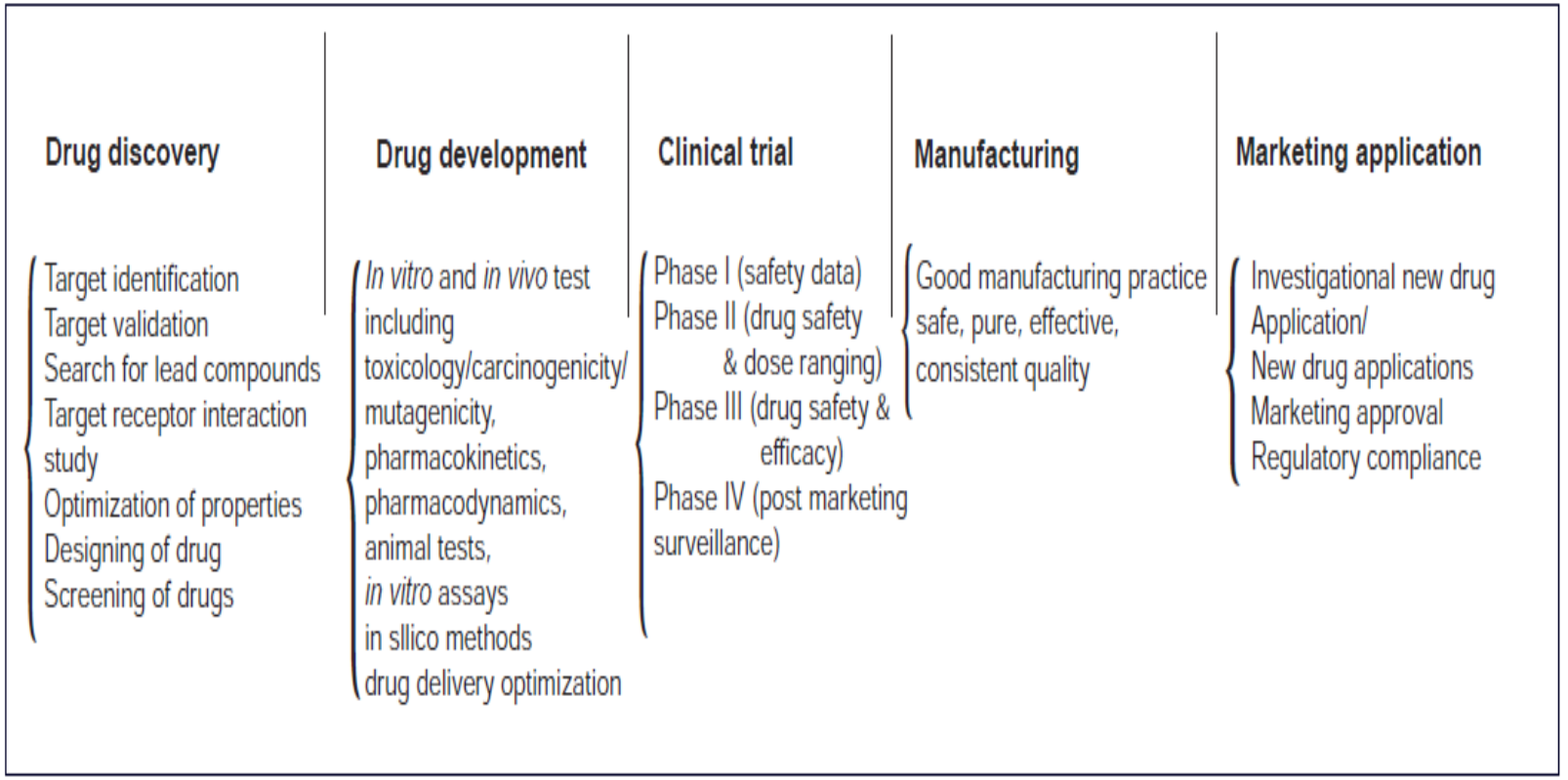
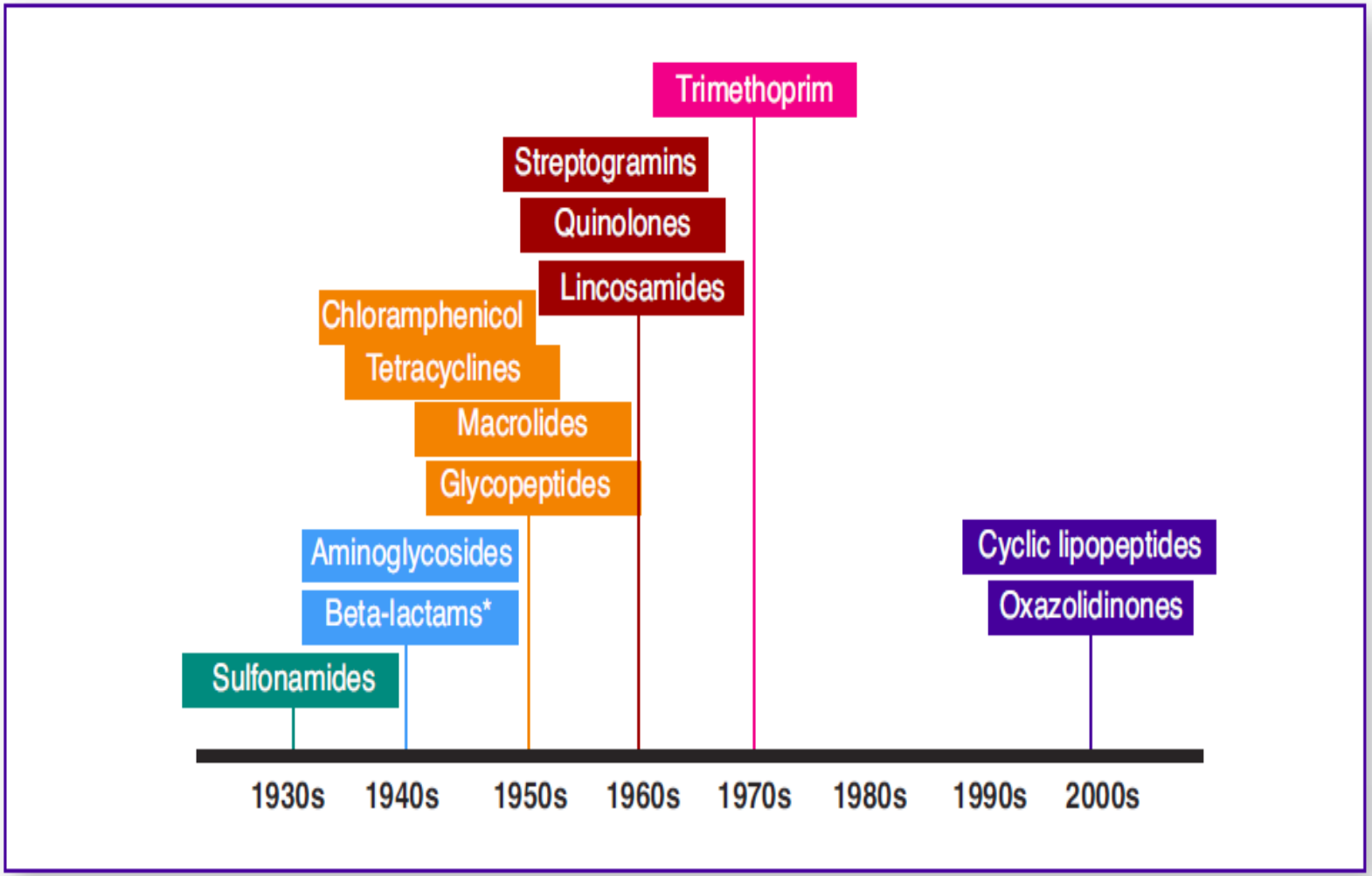
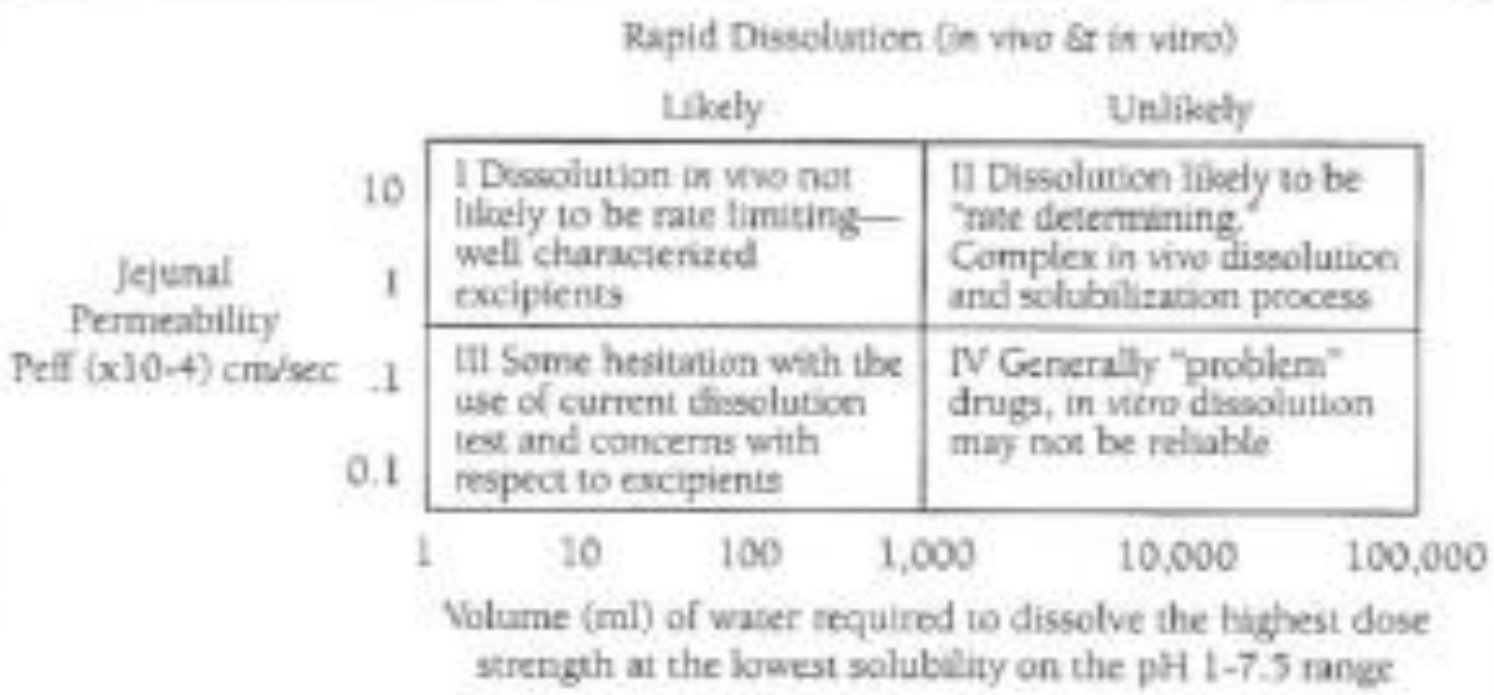


Figure 6.1 Discovery of new classes of antibacterial drugs (1930s to 2000s)



* Penicillins were the first beta-lactams. This class includes cephalosporins and carbapenems, developed in the 1960s and 1980s, respectively.

FIGURE 5-6
BCS CLASS MEMBERSHIP RISK MANAGEMENT



SOURCE: Prabir K. Basu, "Importance of Building in Quality, Need for Industry Progress in this area, Implications for Overseas Outsourcing." NIPTE. http://prescriptionproject.org/assets/pdfs/Basu.pdf.

Resistance selection

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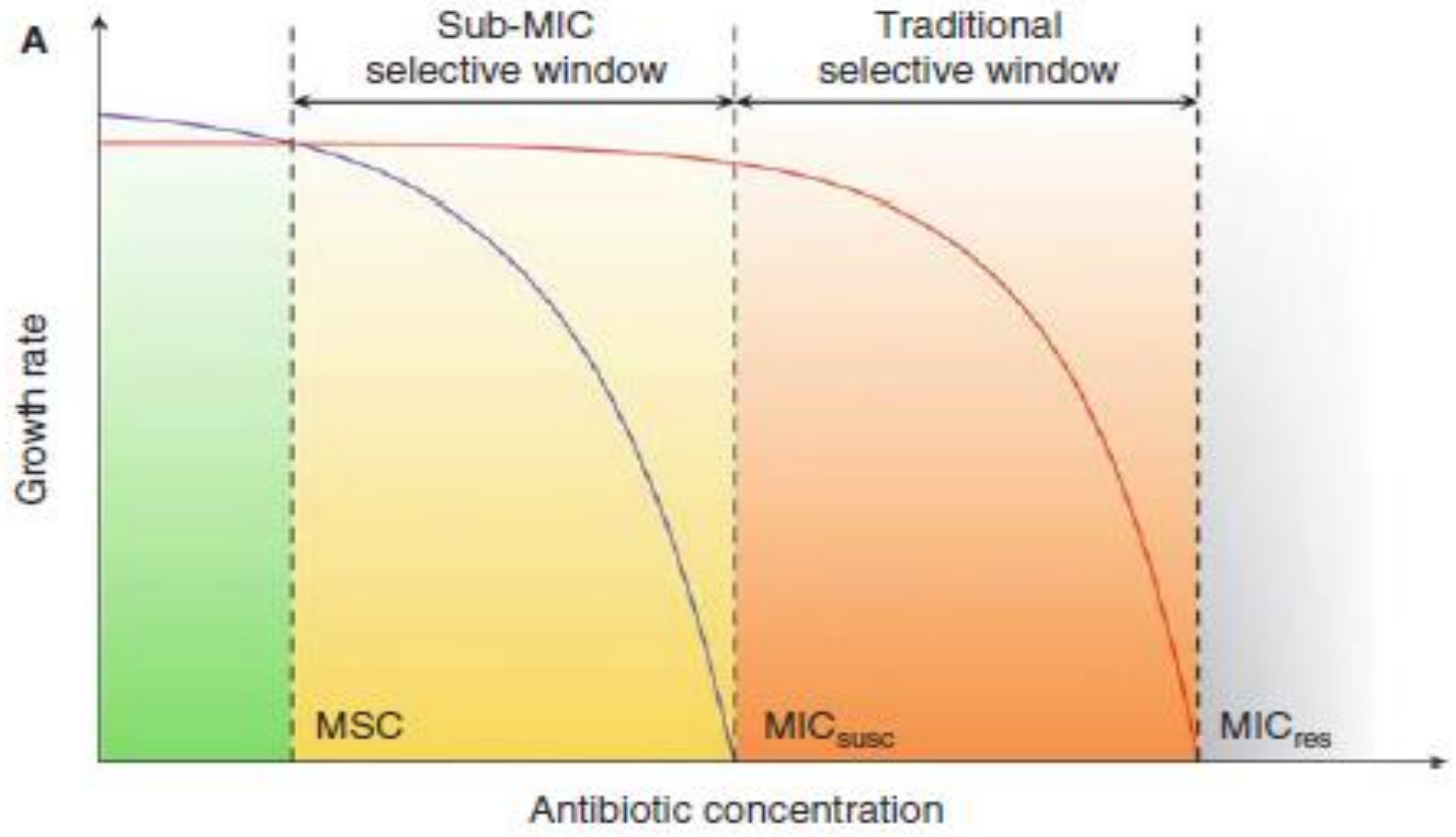

PHAKE

THE DEADLY WORLD OF FALSIFIED AND SUBSTANDARD MEDICINES

ROGER BATE

The less privileged face biggest issues!

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SVEN TORFINN/PANOS

Prevalence of TB in South Africa is among the highest in the world and drug resistance is growing

South Africa withdraws TB drugs because of quality fears

South African health authorities have withdrawn two generic drugs widely used in the country to treat tuberculosis, amid concerns about their quality.

When the health minister, Manto Tshabalala-Msimang, announced the withdrawal earlier this month she said that her department had received information suggesting that the ingredients in the two combination drugs, called Antib-4 and Ebsar, "were not at the level stated in the label after storage."

Antib-4 combines pyrazinamide, ethambutol, isoniazid, and rifampicin. Ebsar is a combination of isoniazid and rifampicin.

Both drugs are manufactured in India by Rusan Pharma and imported into South Africa, where they are registered to another company, MDI.

Generic antimalarial- African sources

Generic Antibiotic Failures in India

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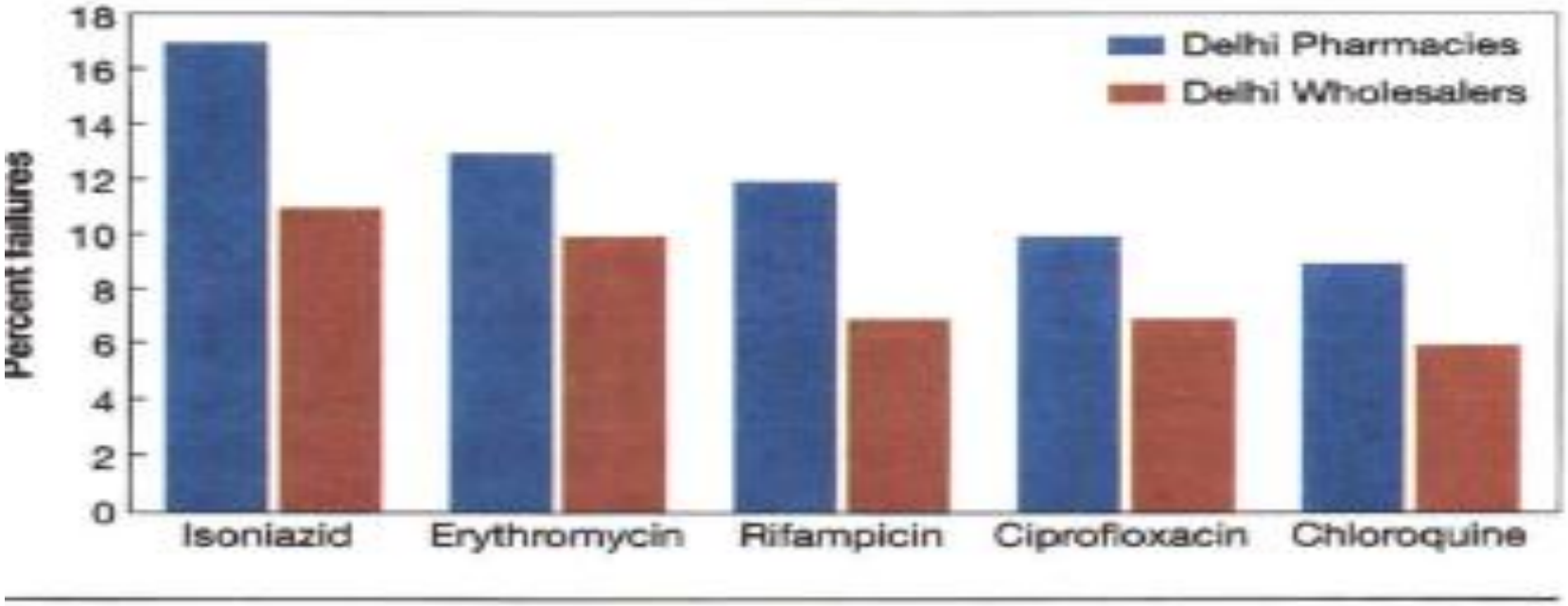
FIGURE 12-3
PERCENT FAILURE BY DRUG TYPE, PHARMACIES VS. WHOLESALERS



Failure Rates of Generic Anti-Infectives

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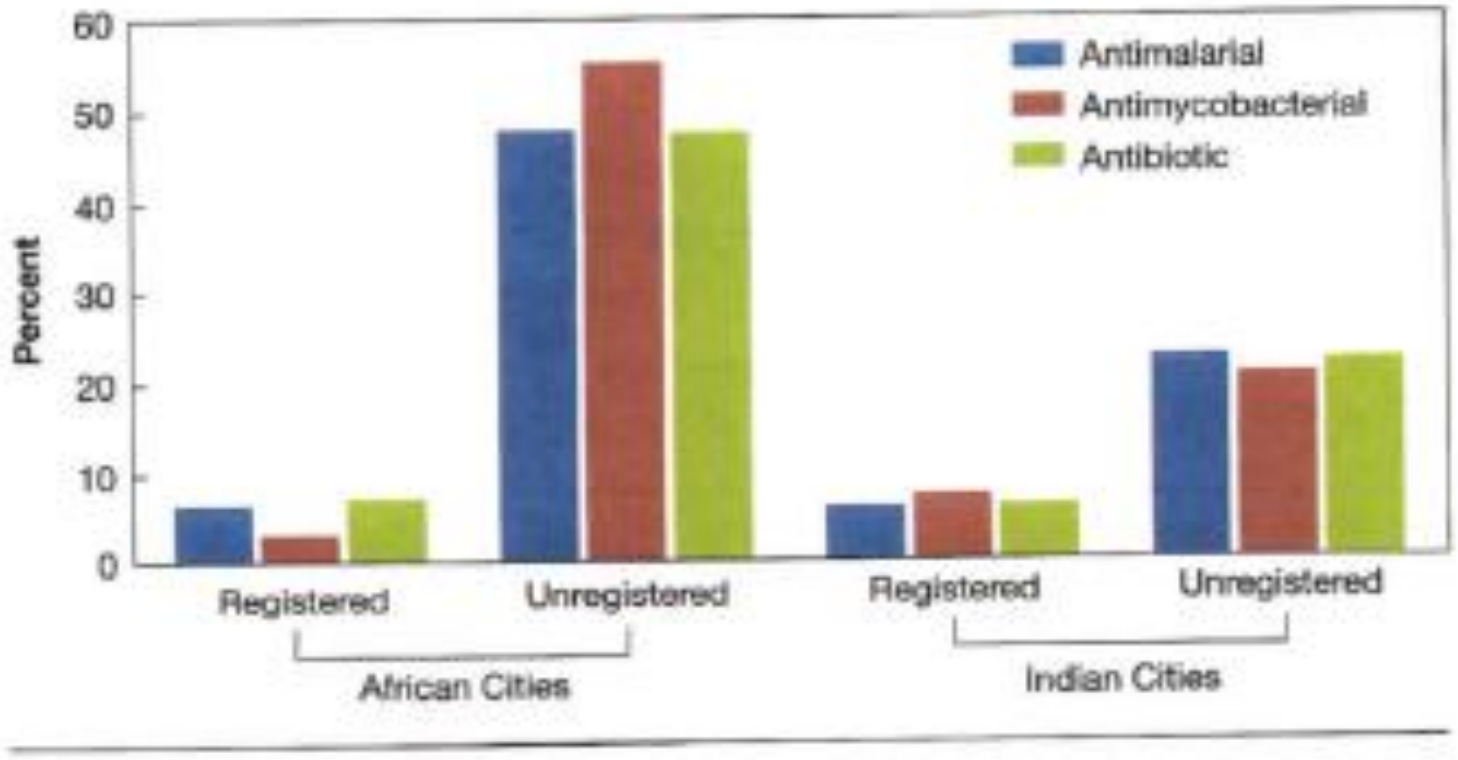
FIGURE 11-3
FAILURE RATE BY REGISTRATION STATUS, TYPE, AND REGION



Generic failure rates by anti-infective-regionally

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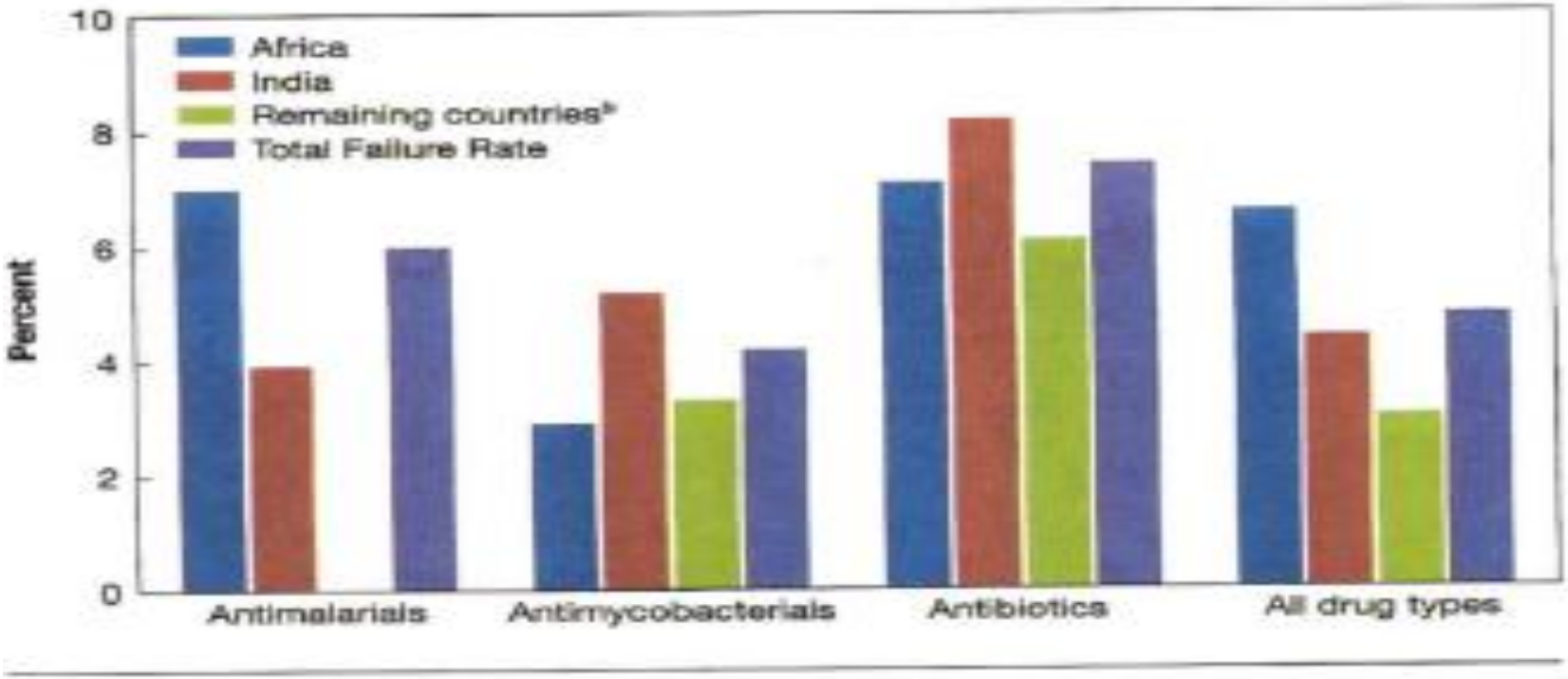
FIGURE 13-1
TESTING RESULTS BY REGION OF ORIGIN AND DRUG TYPE[a]



NOTE: None failed which is why these do not appear on the graph.
a. Percentages are supported by total that failed testing/total samples tested.
b. Remaining countries include Thailand, China, Turkey, Russia, Brazil.

FDA Cases of Overseas drugs

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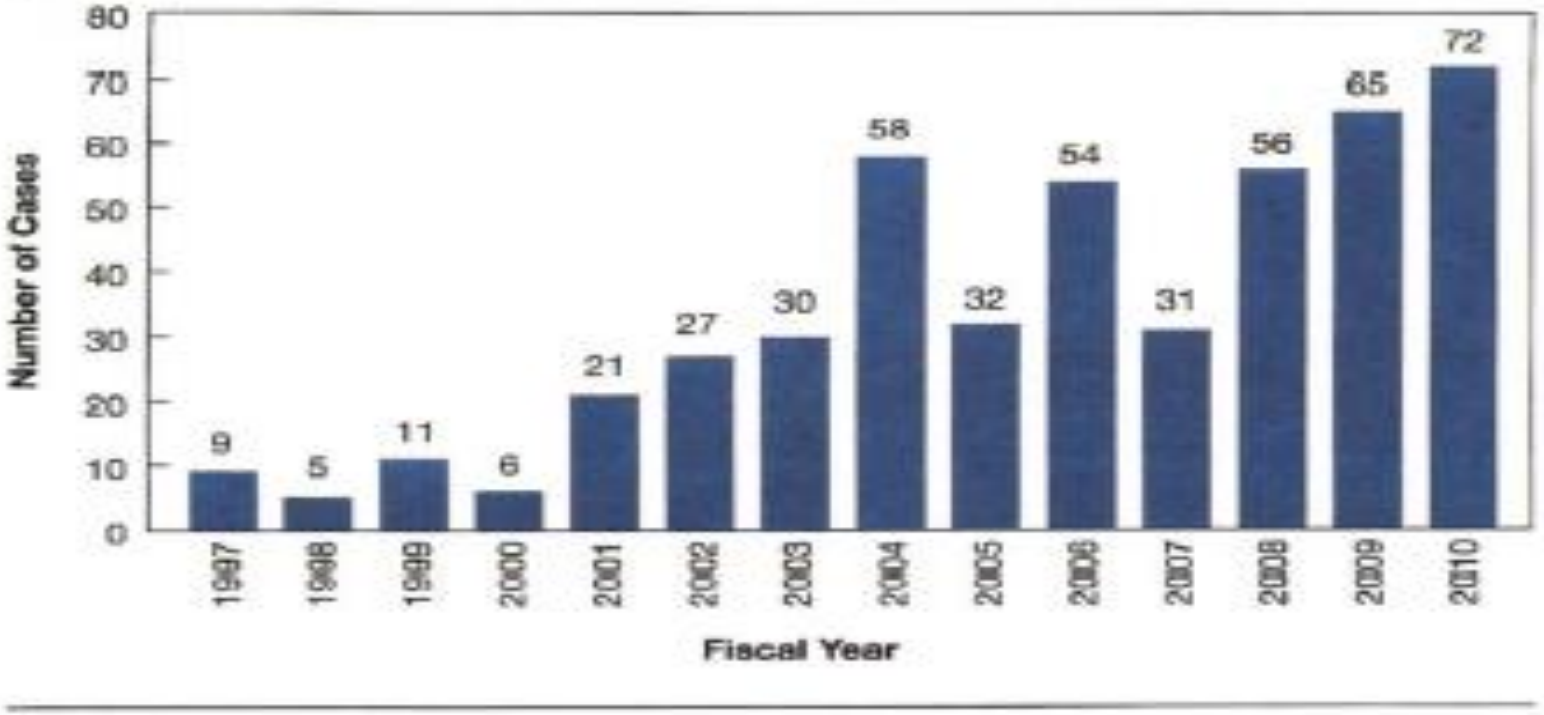
FIGURE 2-4
COUNTERFEIT DRUG CASES OPENED BY
FDA'S OVERSEAS CRIMINAL INVESTIGATION DEPARTMENT



SOURCE: www.fda.gov

Range of API failures by region

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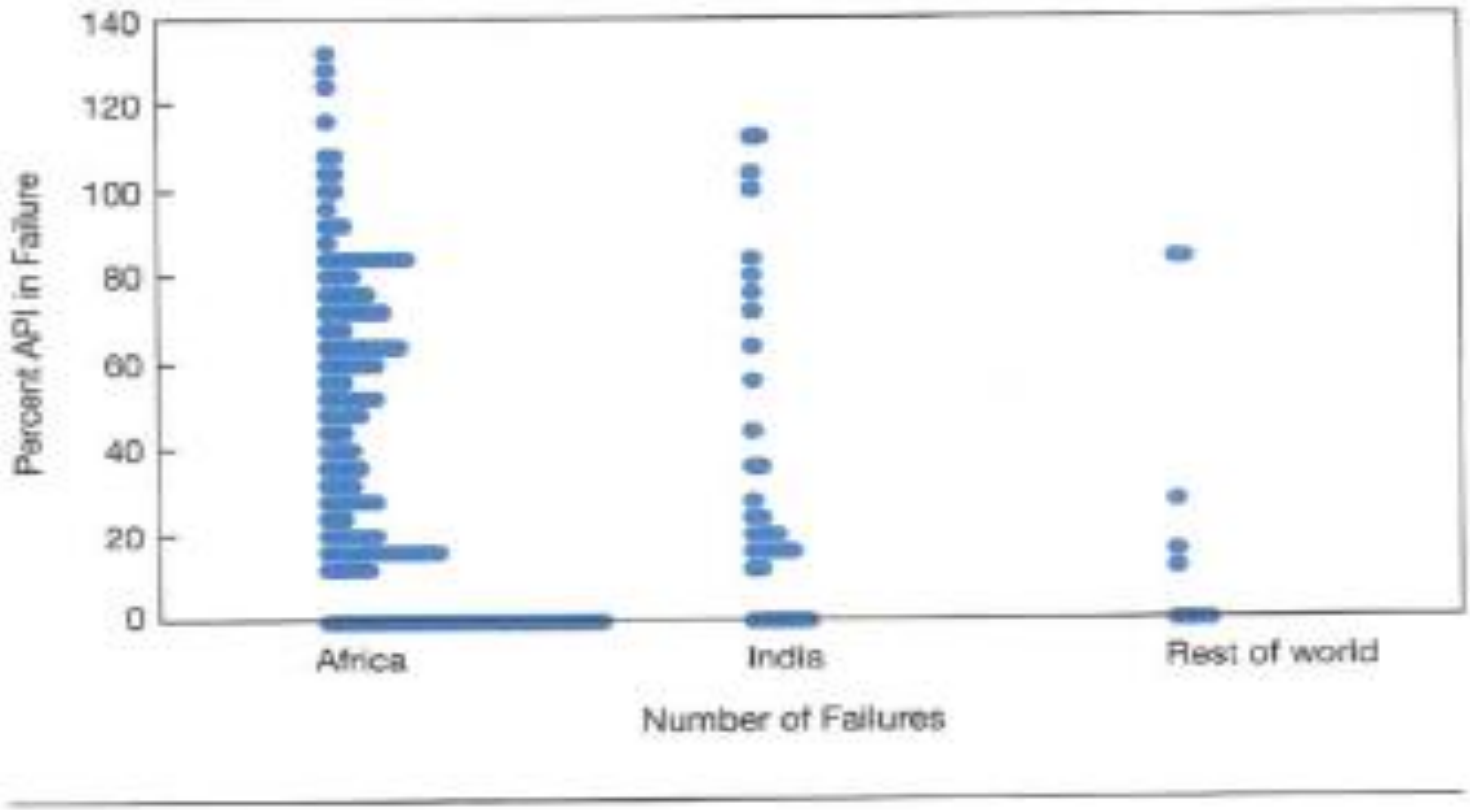
FIGURE 13-3
FAILURES WITH X PERCENT API



Reported cases of aberrant generic antibiotics

- Oxacillin
- Piperacillin-tazobactam
- Clarithromycin
- Gentamicin
- Ciprofloxacin
- Vancomycin

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B-lactams

OXACILLIN, PIPERACILLIN-TAZOBACTAM

Oxacillin generic variability in a mouse model

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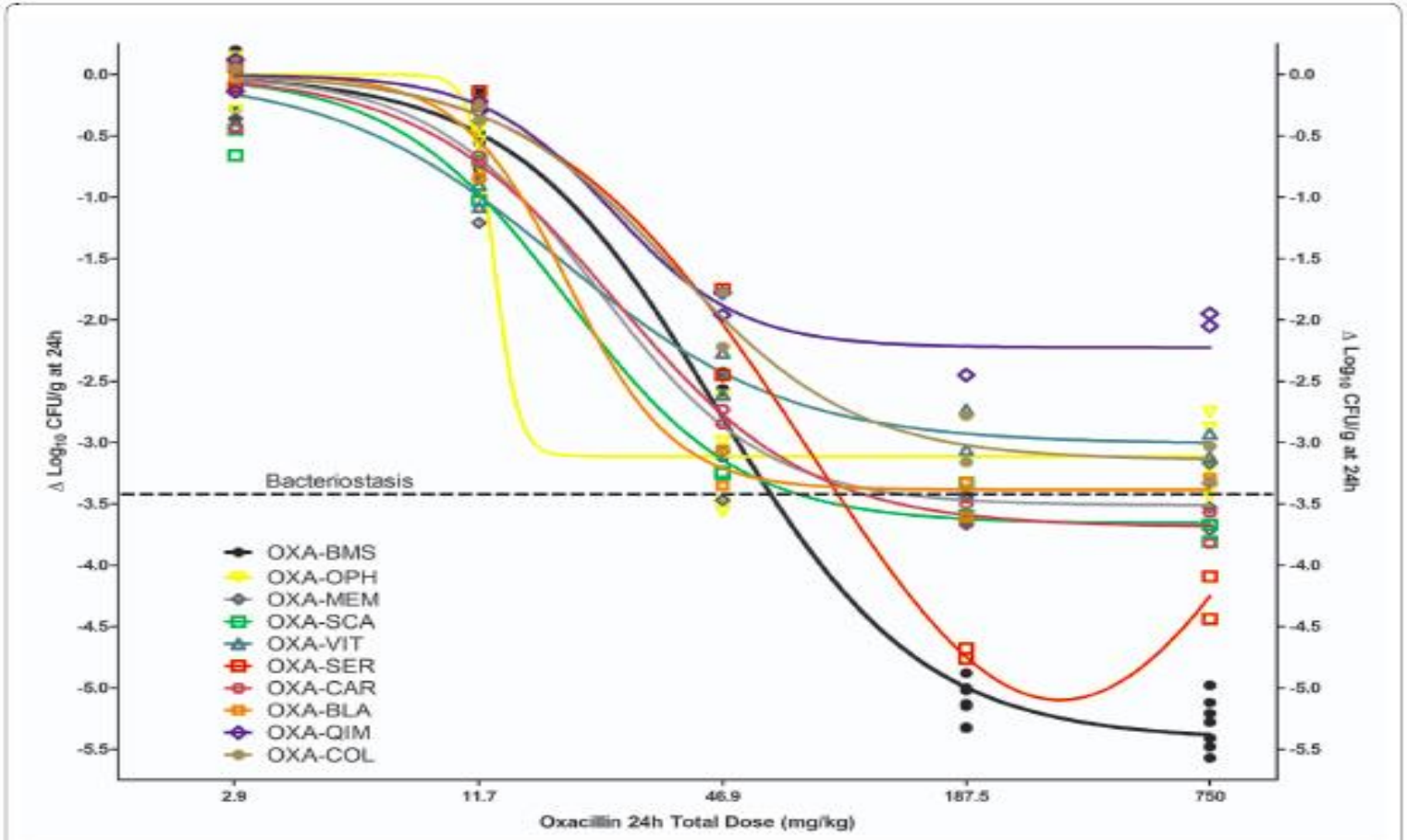

Figure 3 Dose-response relationship of the innovator and 9 generic products of oxacillin in the neutropenic mouse thigh infection model.

Piperacillin/tazobactam Variability

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Table 1
Listing of 23 additional (14 manufacturers) lots of generic intravenous piperacillin/tazobactam formulations screened by a multiorganism in vitro MIC assay[a]

Manufacturer (lot no.)	Product name	Vial strength	Dates		Country of origin	Assay variation (%)[b]
			Expiration	DOT[c]		
Cellofarm (7100789)	Tazpen	4.5 g	01/2009	01/2008	Brazil	−27
Cellofarm (7100794)	Tazpen	4.5 g	01/2009	03/2008	Brazil	−5
Eurofarma (121609C)	Piperacillin/tazobactam	4.5 g	09/2009	01/2008	Brazil	−4[d]
Eurofarma (117968B)	Piperacillin/tazobactam	2.25 g	08/2009	01/2008	Brazil	−11
Eurofarma (126133A)	Piperacillin/tazobactam	2.25 g	12/2009	03/2008	Brazil	−26
Eurofarma (124032E)	Piperacillin/tazobactam	4.5 g	12/2009	03/2008	Brazil	**4**[e]
Novafarma (0760088)	Piperacillin/tazobactam	4.5 g	12/2009	03/2008	Brazil	−18
Novafarma (0760076)	Piperacillin/tazobactam	4.5 g	12/2009	01/2008	Brazil	−27
Farmalogica (11704-1)	Piperacillin/tazobactam	4.5 g	06/2009	09/2008	Colombia	−16
Vitrofarma (B050822)	Vitalis®	4.5 g	05/2010	09/2008	Colombia	−13
SUMI Med (08050434	Piperacillin/tazobactam	4.5 g	01/2010	09/2009	Colombia	−10
Kendrik (6JB030)	Tasovak®	4.5 g	08/2008	01/2008	Mexico	−3
Kendrik (7LB016)	Tasovak®	4.5 g	08/2009	09/2008	Mexico	−13
Teva (A002)	Piperacillin/tazobactam (Teva®)	4.5 g	12/2009	03/2008	Switzerland	−11
Ratiopharm (H22498)	Piperacillin/tazobactam	4.5 g	02/2010	09/2008	Germany	−18
Hospira (B058004)	DBL®	4.5 g	02/2010	03/2009	Australia (India)	−42
Hospira (B088001)	DBL®	4.5 g	10/2010	04/2009	Australia (India)	−14
Orchid (B058005)	Zopercin®	4.5 g	02/2010	03/2009	India	−26
Ibigen (8F06TR)	Ibigen®	4.5 g	05/2010	03/2009	Czech Republic (Italy)	−21
Ibigen (8L12TR)	Ibigen®	4.5 g	07/2010	03/2009	Czech Republic (Italy)	−26
Sandos (155534)	Piperacillin/tazobactam	3.375 g	03/2010	03/2009	Canada	**10**
Stragen (1PT08030)	Piperacillin/tazobactam	2.25 g	10/2010	03/2009	Norway	−15
Stragen (1PT08010)	Piperacillin/tazobactam	4.5 g	10/2010	03/2009	Norway	−16

Potency variations across Pip/Tazo lots

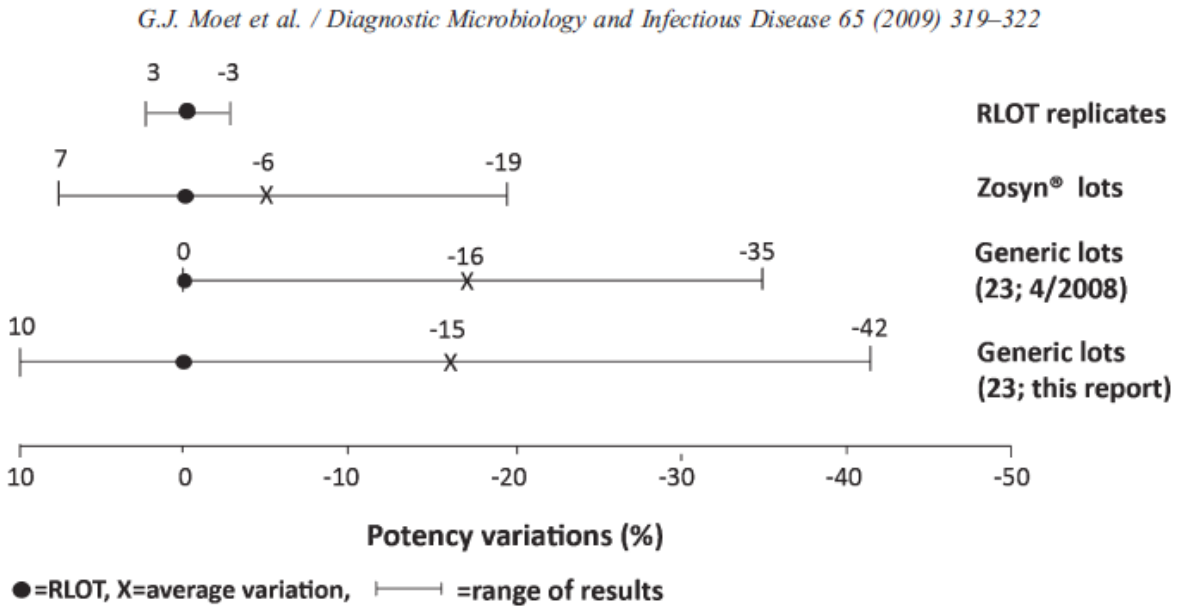

Fig. 1. Extent of potency variations among 4 groups of experiments with piperacillin/tazobactam intravenous injection lots.

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Ciprofloxacin

WORLD VIEW

Variability in the content of Indian generic ciprofloxacin eye drops

R E Weir, F H Zaidi, D G Charteris, C Bunce, M Soltani, A M Lovering

Br J Ophthalmol 2005;**89**:1094–1096. doi: 10.1136/bjo.2004.059519

130 samples of ciprofloxacin eye drops bought from around India.
30 were randomly chosen to be examined.
Two different analytical methods were used to assess the products.

Conclusions: Approximately 20% of generic ciprofloxacin eye drops, purchased without prescription in India were under-potent. In a number of preparations the antibiotic content was sufficiently low as to have a potential impact on clinical outcome and possibly lead to the selection of resistant isolates in individual patients. More widespread studies are justified to identify the extent of under-potency of widely used generic antibiotic medications in developing countries.

Fake Ciprofloxacin

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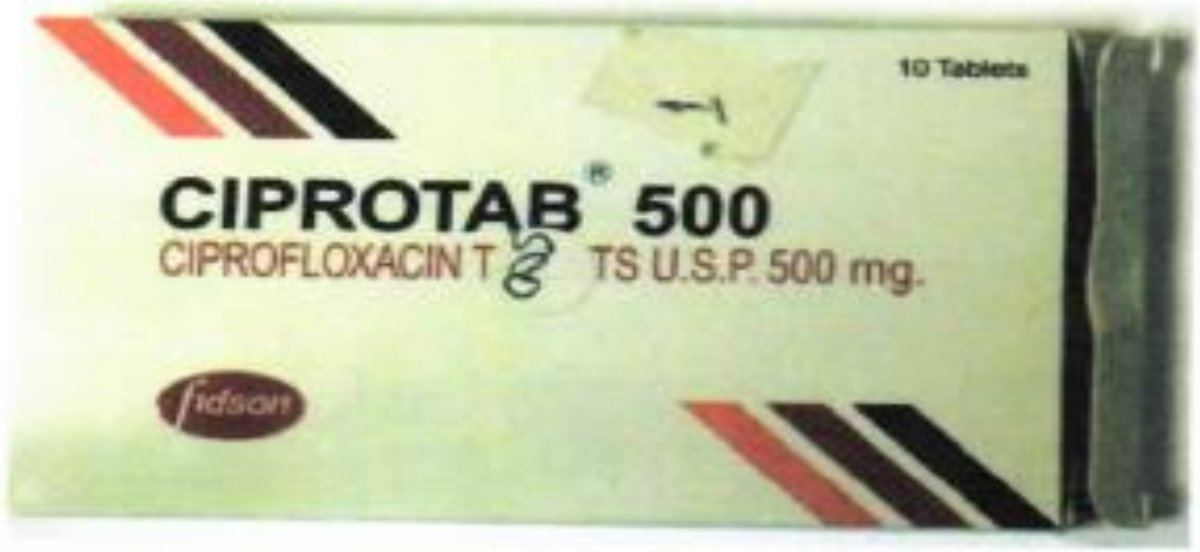
FIGURE 5-3



Ciprotab fake package

Changes in USA: Ciprofloxacin Resistance & Shigella species

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Escalating ciprofloxacin resistance in Shigella in USA

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Increasing Ciprofloxacin Resistance Among US Shigellosis Outbreaks

Drug-resistant *Shigella sonnei* infections in the United States have been linked with international travelers who repeatedly transmit the bacterium domestically, leading to an increasing proportion of US shigellosis cases that are resistant to the first-line antibiotic treatment, ciprofloxacin.

Recent outbreaks of ciprofloxacin-resistant shigellosis sickened 243 people in 32 states and Puerto Rico between May 2014 and February 2015. About half of the infections were associated with international travel, mostly to the Dominican Republic and India. Ninety-five of the cases were in San Francisco, where a ciprofloxacin-resistant shigellosis outbreak was linked with the homeless population or people living in single-room occupancy hotels.

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Clarithromycin

Generic clarithromycin- Slovenia & Israel

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ABSTRACT

This study evaluated the quality of 11 generic clarithromycin products obtained in Poland, Slovakia, Slovenia, or Israel and manufactured in Slovenia or Israel. The generic products were examined visually, assayed by high-pressure liquid chromatography for clarithromycin content and impurities, tested for dissolution properties, and compared with the innovator product manufactured by Abbott Laboratories. Fifty-five percent of generic products fell short of the specifications for the innovator product. Ten percent of the generic products did not contain the amount of clarithromycin claimed in the label; 18% released less drug than did the branded tablets in the standard dissolution assay. In light of these results, it is not possible to conclude that all generic tablets are of the same quality as the innovator product; clinical trial results achieved with branded clarithromycin should not be extrapolated to generic products.

Dissolution rates for generic clarithromycin

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Table 5. Dissolution Results

Sample	Product	Country	Mean % Dissolved at 30 minutes*	Range, %
Reference	Klacid (250 mg)	Uruguay	95	93–98
Reference	Klacid (500 mg)	Brazil	94	90–98
Generic products				
1	Fromilid	Slovenia	82	79–85
6	Fromilid	Slovenia	83	80–85
3	Fromilid	Slovenia	89	86–92
2	Fromilid	Slovenia	89	88–92
8	Fromilid	Slovenia	90	88–92
7	Fromilid	Slovenia	94	90–97
4	Fromilid	Slovenia	94	92–97
10	Karin	Israel	94	92–96
9	Fromilid	Slovenia	95	93–98
11	Klarin	Israel	98	96–99
5	Fromilid	Slovenia	99	96–101

*USP specifications require release of at least 85% of the drug in 30 minutes.

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Gentamicin

Determination of Therapeutic Equivalence of Generic Products of Gentamicin in the Neutropenic Mouse Thigh Infection Model

Andres F. Zuluaga[1,2], Maria Agudelo[2], John J. Cardeño[2], Carlos A. Rodriguez[1,2], Omar Vesga[1,2,3]*

1 Department of Pharmacology and Toxicology, University of Antioquia Medical School, Medellín, Colombia, **2** Grupo Investigador de Problemas en Enfermedades Infecciosas, University of Antioquia Medical School, Medellín, Colombia, **3** Section of Infectious Diseases, Department of Medicine, Hospital Universitario San Vicente de Paul and University of Antioquia Medical School, Medellín, Colombia

		Generic Product Failure	
Batch Group	**Gentamicin Generic Product**	**In vitro**	**In vivo**
1	Abbott	No	Yes
(same batch tested in vitro and in vivo)	Biochemie	No	Yes
	Colmed	No	Yes
	Gencol	No	Yes
	Lab America	No	No
	Merck	No	Yes
	Ophalac	No	No
	Rande	No	No
	Servipharm	No	No
	Sigma	No	Yes

In vivo outcomes of gentamicin treatment of neutropenic mouse thigh model.

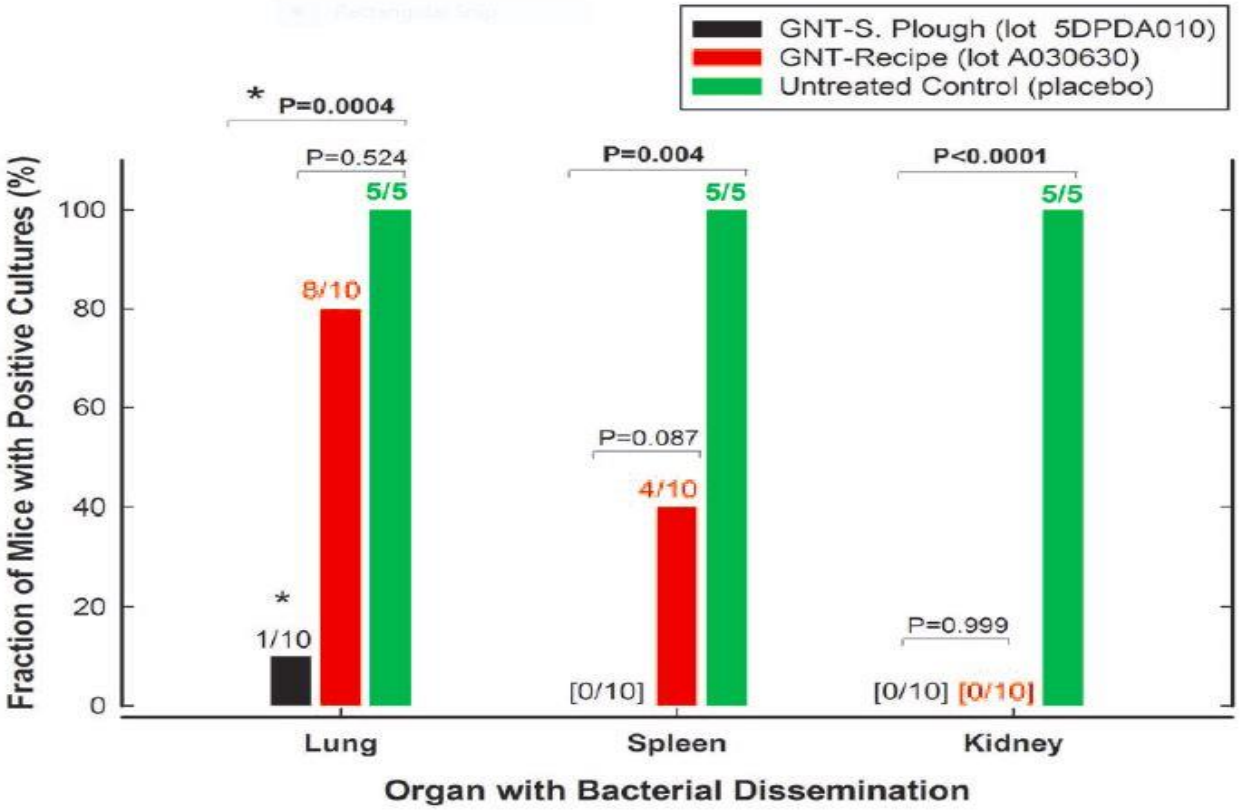

Figure 5. Bacterial dissemination to distant vital organs during survival experiments.

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Vancomycin

Vancomycin – a complete story

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- Proven pharmaceutical inequivalence between batches of generic vancomycin
- Hypothesis that poor batches can select for resistant MRSA in mouse model
- Human clinical failure reported with generic vancomycin corroborated with clinical success with innovator agent.

TABLE 1. Characteristics of vancomycin products

Vancomycin product	Form	Label	Batch/lot no.	Manufacturer	Importer
Lilly (innovator)	0.5 g powder for i.v. injection	Vancocin CP	A050370, A048213, A014744	Eli Lilly & Compañia de Mexico SA de CV	Eli Lilly Interamericana Inc., Bogota, Colombia
		Vancocina CP	5MJ42M, 5MT38P, 5MT66 M	Eli Lilly & Company, Indianapolis, IN	Eli Lilly Interamericana Inc., Bogota, Colombia
Abbott	0.5 g powder for i.v. injection	Sterile vancomycin hydrochloride, USP	18879Z7, 95826Z72	Abbott Laboratories, North Chicago, IL	Abbott Laboratories de Colombia SA, Bogota, Colombia
		Vancomicina IV	19236TB21, 22826TB21, 83858Z7	Abbott France, France	Abbott Laboratories de Colombia SA, Bogota, Colombia
		Vancomicina IV	85739Z7, 03703Z7, 09993Z7	Abbott Laboratories, North Chicago, IL	Abbott Laboratories de Chile Ltda., Santiago, Chile
APP	0.5 g and 1 g powder for i.v. injection	Vancomycin hydrochloride, USP	121384, 120331, 120740	American Pharmaceutical Partners Inc., Los Angeles, CA	Comedica Ltda., Bogota, Colombia
Proclin	0.5 g powder for i.v. injection	Vancomicina 500 mg	6679, 8872, 8690, 8441, 11471, 10049	Laboratorios Northia S.A.C.I.F.I.A., Argentina	Proclin Pharma SA, Bogota, Colombia

Generic Vancomycin Enriches Resistant Subpopulations of *Staphylococcus aureus* after Exposure in a Neutropenic Mouse Thigh Infection Model

Carlos A. Rodriguez,[a,b] Maria Agudelo,[a,b] Andres F. Zuluaga,[a,b] and Omar Vesga[a,b,c]

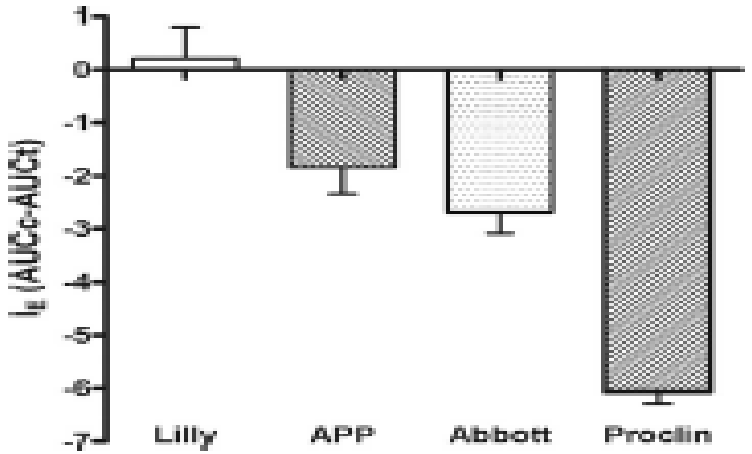

FIG 4 Overall changes in the AUC (intensity of the effect I_E) after exposure to innovator (Lilly) and generic (APP, Abbott, and Proclin) vancomycin products compared with the control group. Positive values indicate smaller AUCs, i.e., a reduction of less susceptible subpopulations with Lilly, while negative values indicate greater AUCs, i.e., enrichment of resistant subpopulations, with APP, Abbott, and Proclin (ANOVA, $P < 0.0001$; all comparisons of a generic versus the innovator compound had a P value of <0.05 by Dunnett's posthoc test).

Journal of Infection (2009) 59, 277–280

www.elsevierhealth.com/journals/jinf

CASE REPORT

Potential therapeutic failure of generic vancomycin in a liver transplant patient with MRSA peritonitis and bacteremia

Carlos A. Rodriguez [a,b], Maria Agudelo [a], Juan C. Cataño [c], Andres F. Zuluaga [a,b], Omar Vesga [a,c,*]

Summary We report a case of generic vancomycin treatment failure in a liver transplant patient with MRSA peritonitis and bacteremia, followed by a rapid sterilization of blood and peritoneal fluid after switching to the branded product. It raises concern about therapeutic equivalence of generic vancomycin.

So are local sub-standard antibiotics a local issue?

- Inadvertent misuse of antibiotics- poverty or access

AVOID LOW QUALITY AND SUB-STANDARD DRUGS; PREVENT PRESCRIPTION CHANGES AT THE DRUGSTORE

Terms "low quality" and "sub-standard" are used here to refer to generic drugs that do not meet the requirements of bioequivalence (98–102% of active ingredient as labeled, 85–125% of maximum plasma concentration, C_{max}, and time-concentration area under the curve, AUC, of the original drug). Unfortunately, even those minimal requirements are not considered by national health authorities of many countries. Bioequivalence is not necessarily a test for clinical efficacy (Vesga et al., 2010); furthermore, lack of quality control, corruption, counterfeit drugs, deficient control at drugstores, etc. (Newton et al., 2010), common in developing countries, diminish the confidence on generic drugs. Additionally, even in developed countries, generic drugs are sub-standard (Del Tacca et al., 2009). Low quality ATB may result in pharmacokinetic profiles much different from the ones of original drugs which, in turn, may create increased periods of time of sub-inhibitory concentration exposure, leading to treatment failure and/or resistance. This is not, of course, a problem plaguing all generic drugs; many products have shown to be bioequivalent to original ones (Mazur et al., 1999; Galan-Herrera et al., 2009). But the "burden of evidence" should rely on generic manufacturers, which should demonstrate clinical efficacy instead of only bioequivalence. In many countries it is also a common practice from drugstore salespeople to change physicians' prescriptions. Physicians must alert patients of this practice, which is also a risk for a complete change of drug or modified-release formulation. (The working group that

So are local sub-standard antibiotics a local issue?

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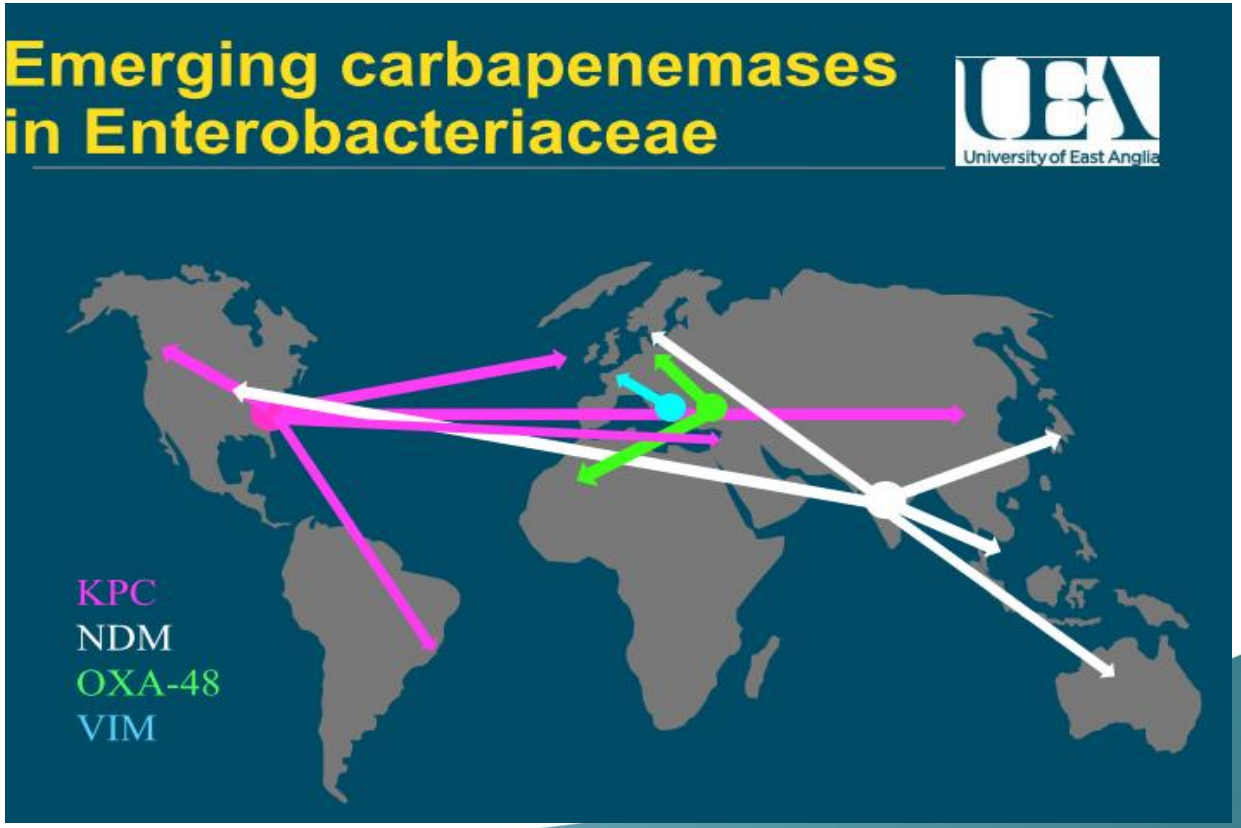
- Inadvertent misuse of antibiotics- poverty or access
- Global travel

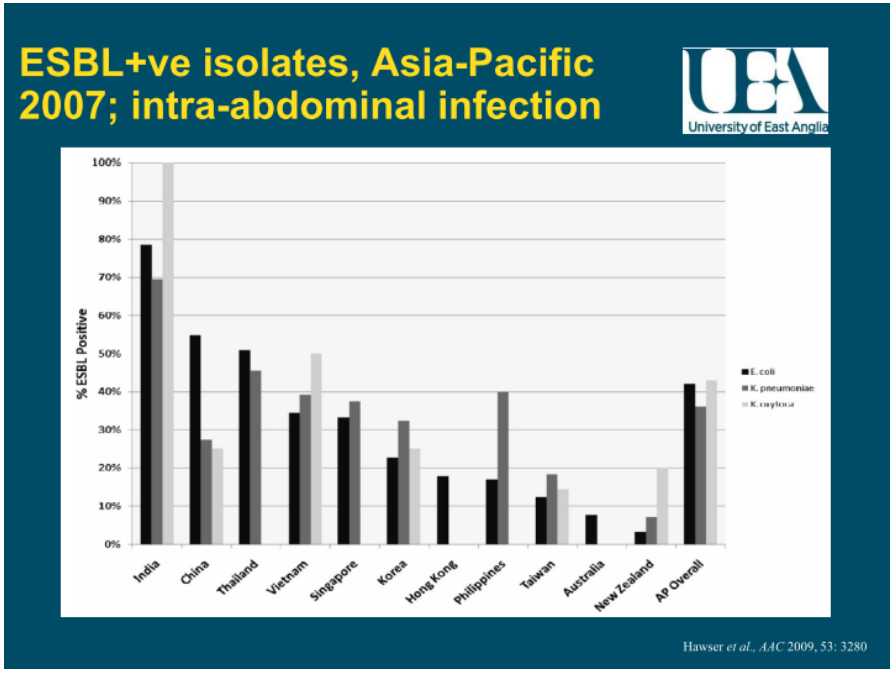


- Natural phenomenona

E. coli

Asia-Pacific - Highest Levels of ESBL+

Incidence of ESBL+ isolates in cIAI infections:
Africa 8.3%, Asia 42.5%, Europe 16.5%, Middle East 23.5%, N. America 6.8%



Source: Livermore D One Bug One Drug Conference Cambridge, UK, 24 September 2013, Hackel M et al Poster 774, ID week October 2013

N. gonorrheae

World Wide Issue – CDC Treat 'Urgent'

- WHO estimates 106 million new cases of N. gonorrheae in 2008.
  - Gonorrhea is the second most commonly notified disease in the US. CDC estimate up to 820,000 cases per year (~320,000 reported).
  - Only 32,000 cases were reported in EEA/EU countries (most reported in UK - not a notifiable disease in Europe).
- N. gonorrheae has a long history of world wide resistance development to ever more classes of antibiotics.

	Percentage	Estimated number of cases
Gonorrhea		820,000
Resistance to any antibiotic	30%	246,000
Reduced susceptibility to cefixime	<1%	11,480
Reduced susceptibility to ceftriaxone	<1%	3,280
Reduced susceptibility to azithromycin	<1%	2,460
Resistance to tetracycline	23%	188,600

Source: The Gonococcal Isolate Surveillance Project (GISP)–5,900 isolates tested for susceptibility in 2011.

Source: Global Incidence & Prevalence of Curable STIs -2008, WHO; Antibiotic Resistance Threats in the US 2013, CDC

So are local sub-standard antibiotics a local issue?

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- Inadvertent misuse of antibiotics- poverty or access
- Global travel
- Natural phenomenon

Worldwide spread of NDM-1: are migratory birds culprits?

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Key words: NDM-1; migratory birds; drug resistance.

J Infect Dev Ctries 2015; 9(1):120-121. doi:10.3855/jidc.5294

Conclusions

- Established chemical methods for generic antibiotics are insufficient to prove equivalence to innovator product
- Impact of less active generic antibiotics poses resistance selection threat
- Animal models have proven clinical non-equivalence with a range of antibiotic classes
- Clinical failures have been reported but hard to prove at health system or country level.

(Mazur et al., 1999; Galan-Herrera et al., 2009). But the "burden of evidence" should rely on generic manufacturers, which should demonstrate clinical efficacy instead of only bioequivalence. In