The diagnosis-treatment gap: lessons from the field.

Erika Vlieghe

Institute of Tropical Medicine Antwerp (Belgium)

ISC Antibiotic Stewardship Working Group

- ‘ I am not ‘the’ expert, just part of a team trying to put theory into practice…’

Our partners…

Africa, Asia, South-America

République Démocratique du Congo	Institut National de Recherche Biomédical	Reference function + Research
Phnom Penh, Cambodia	Sihanouk Hospital Centre of HOPE	NGO-Hospital, HIV/TB
Lima, Peru	Instituto de Medicina Tropical	Research

Our approach…

1. **Laboratory** Infrastructure, Training, Quality (ISO 15189 accreditation)

   Surveillance of Resistance: cohort-based

2. **Antibiotic Stewardship**: Standard Treatment Guidelines, Education, Infection Control

Review

International Journal of Antimicrobial Agents 34 (2009) 295–303

Antibiotic resistance among bacterial pathogens in Central Africa: a review of the published literature between 1955 and 2008

E. Vlieghe[a,*], M.F. Phoba[b], J.J. Muyembe Tamfun[b], J. Jacobs[a]

[a] Department of Clinical Sciences, Institute of Tropical Medicine, Nationalestraat 155, 2000 Antwerp, Belgium
[b] Institut National de Recherche Biomédicale (INRB), Avenue de la Démocratie (ex Huileries), Kinshasa/Gombe B.P. 1197 Kinshasa 1, Democratic Republic of the Congo

Antibiotic resistance surveillance in theory…

- Essential element in WHO plan for containment of antimicrobial resistance (2001)

- Data needed for:
  - Assessment of scope of AB resistance at local, national, regional level
  - Evidence for locally adapted treatment guidelines
  - Monitor the impact of interventions
  - Monitor emergence of new resistance patterns

- Several types of surveillance:
  - Active/passive
  - focused/comprehensive
  - …

Surveillance programs in practice…

- **Expensive and painstaking**, requires
  - Quality assured and sustainable laboratories
  - Systematic prospective sampling and data collection

- Biased towards **richer countries/areas**
  - With (more) microbiological laboratories
  - Urbanised/accessible areas

- Biased towards **specific pathogens** (fitting in specific 'vertical' programs with own funding)
  - '1 pathogen, 1 disease' (e.g. malaria, TB, HIV)
  - 'fashionable' (e.g. H1N1, neglected tropical diseases,…)
  - Epidemic driven (e.g. *Vibrio cholerae*, *Shigella* spp.,…)

- Available **data often not known/used** by local clinicians

Achilles' tendon = microbiology lab

STRENGTHS	OPPORTUNITIES
• The essential tool for better diagnosis and care • Key to knowledge on AB resistance • Imput in prescribers' knowledge	• Generated data can create awareness • Link AB resistance to existing programmes (e.g. TB, HIV) • Newer rapid diagnostic tests • Internet for learning and feedback • Partnerships (N/S, public/private)
WEAKNESSES	**THREATS**
• 'Image problem' • Drs are not used to working with labs • Lack of internal/external quality control • Not 'cost effective' • Bacterial diseases = diverse and complex • Little collaboration between labs	• Funding for equipment, consumables, salaries, infrastructure • Lack of training/skilled lab technicians • Competition from vertical programs • Donor agendas

Laboratory Medicine in Africa: A Barrier to Effective Health Care

Clinical Infectious Diseases 2006; 42:377–82

Cathy A. Petti,[1,2] Christopher R. Polage,[2] Thomas C. Quinn,[3,4] Allan R. Ronald,[5] and Merle A. Sande[1]

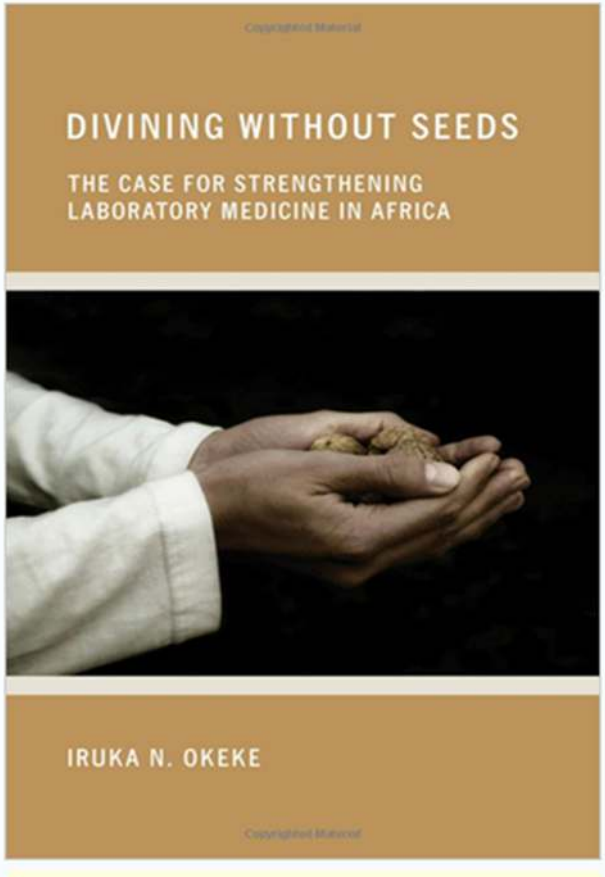
[1]Departments of Medicine and Pathology, University of Utah School of Medicine, and [2]ARUP Laboratories, Salt Lake City, Utah; [3]Department of Medicine, Johns Hopkins School of Medicine, Baltimore, and [4]Laboratory of Immunoregulation, National Institute of Allergy and Infectious Diseases, Bethesda, Maryland; and [5]Faculty of Medicine, University of Manitoba, Winnipeg, Canada

Are Laboratory Services Coming of Age in Sub-Saharan Africa?

CID 2006:42 (1 February) • EDITORIAL COMMENTARY

Imelda Bates[1] and Kathryn Maitland[2,3]

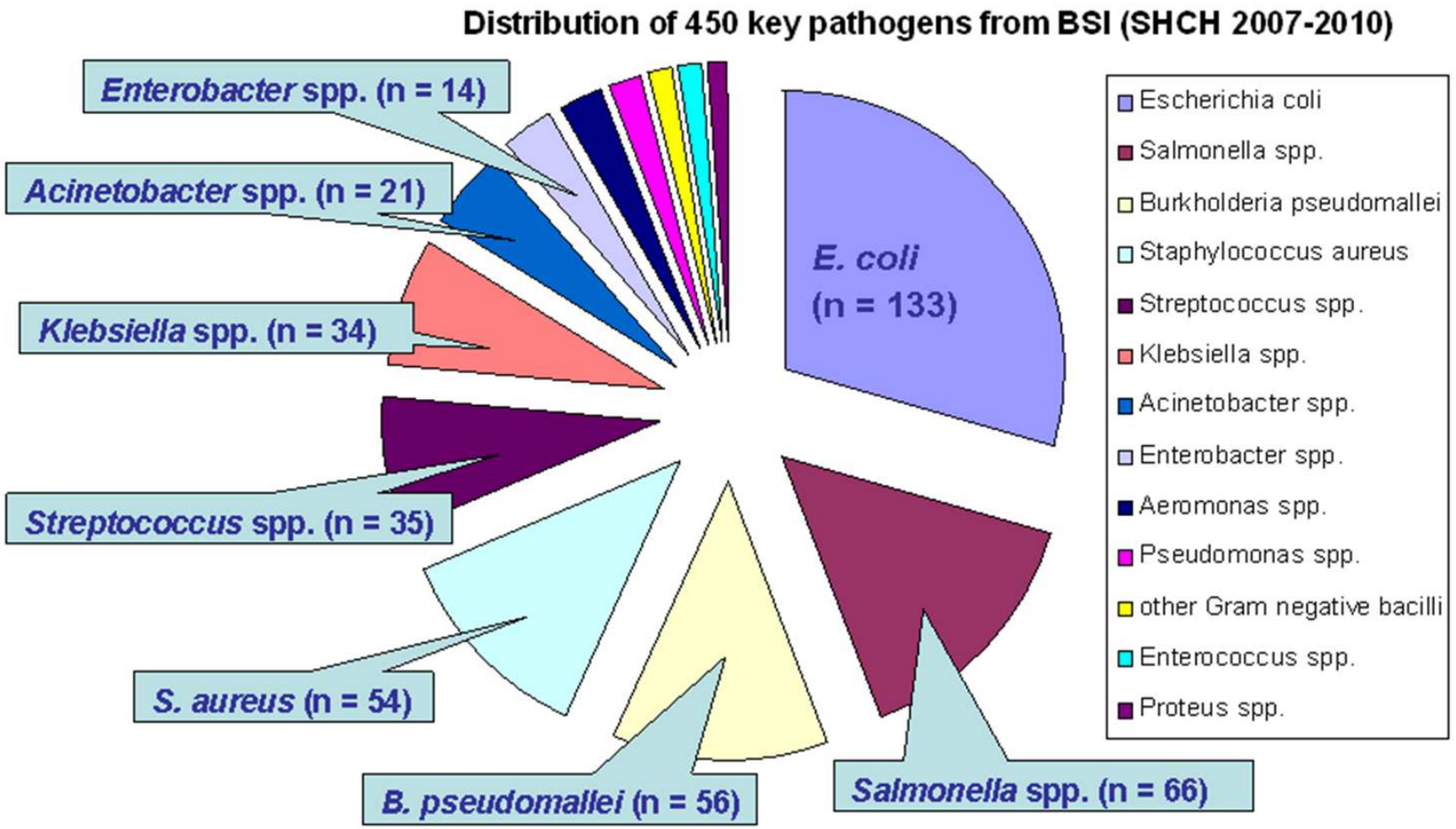
[1]Tropical Haematology, Liverpool School of Tropical Medicine, Liverpool, and [2]Imperial College of the United Kingdom, London, United Kingdom; and [3]T for Geographic Medicine Research, Kenya Medical Research Institute, Kilifi, Kenya



The project's experience

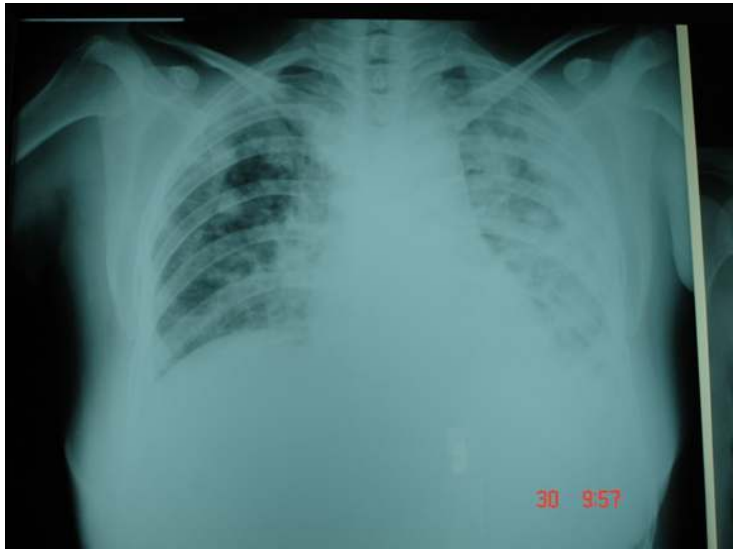
- Supporting small scale laboratories
- Training and internal/external quality control
- Regular feedback & education sessions
  - For laboratory technicians
  - For physicians
- Compiled data = small scale but relevant pilot data

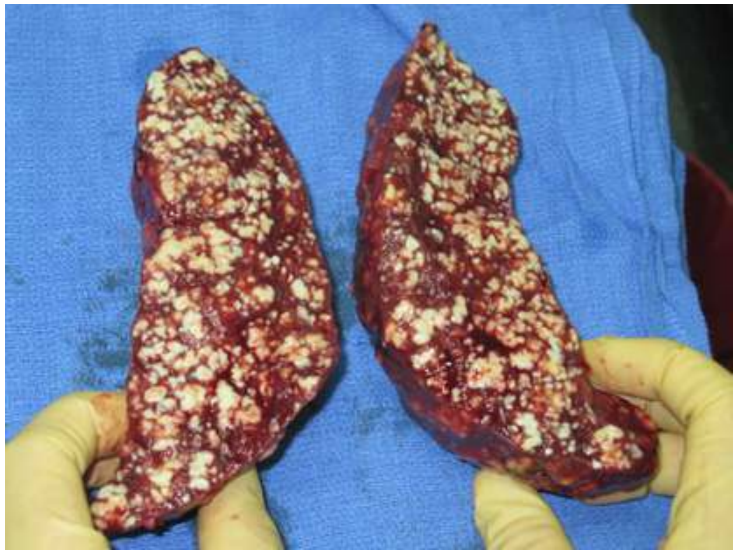
Blood stream infections in Cambodia: surveillance data at-a-glance



BSI Cambodia: 1/8 is *Burkholderia pseudomallei*

- Gram negative NF rod
- Present in soil, water
- SEA region and N Australia
- May cause:
  - Pneumonia
  - abscesses (skin & solid organs)
  - BSI +/- septic shock
- Diabetics
- Wet season





Dance 2002; White 2003; Cheng 2005

Burkholderia pseudomallei

- Effective antibiotics:
  - Ceftazidime, carbapenems, SMX-TMP
  - Amoxycillin-clavulanic acid, (doxycyclin)

- Outcome in 58 patients (Phnom Penh) worse if
  - Presenting with BSI, shock, MOF
  - Inappropriate empirical therapy (e.g. ciprofloxacin, ceftriaxone,…)

- **Need adaption of treatment guidelines for sepsis, pneumonia, …**

- Most local HCW unfamiliar with pathogen before…

Transactions of the Royal Society of Tropical Medicine and Hygiene (2008) 102/S1, S21–S25

A first report of pulmonary melioidosis in Cambodia

Rob Overtoom[a,b]*, Virak Khieu[b], Sopheak Hem[b], Philippe Cavailler[b], Vantha Te[c], Sarin Chan[b], Phea Lau[c], Bertrand Guillard[b], Sirenda Vong[b]

Am. J. Trop. Med. Hyg., 82(6), 2010, pp. 1106–1112
doi:10.4269/ajtmh.2010.10-0030

- **2008: first report**
- **2010-2011: > 200 patients described nationwide**
- **09/2010: First National Workshop on melioidosis (Phnom Penh)**
- **… much more work to be done..**
- **? Availability of ceftazidime nation wide**

Penh, Cambodia

Erika Vlieghe, Lim Kruy, Birgit De Smet, Chun Kham, Chhun Heng Veng, Thong Phe, Olivier Koole, Sopheak Thai, Lut Lynen, and Jan Jacobs

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 7, July 2011

BSI: 1/3 is *E. coli*

- 47.4 % ESBL positive
- High % resistance to first line AB
- First line treatment of sepsis:
  - From ampicillin/gentamicin…. To…?
    - carbapenem? Availability, policy, cost, resistance…?
    - ceftriaxone + amikacin ? Efficacy, cost,…?
    - …?
- 11/2011: National conference on AB resistance

Table 1. Resistance patterns in *Enterobacteriaceae

Antibiotic	*E. coli* (n = 133)	*Klebsiella* spp. (n = 34)	*Enterobacter* spp. (n = 14)
	% resistant isolates		
Ampicillin	93,2	100,0	100,0
Amoxicillin/clavulanic acid	48,1	29,4	85,7
SMX-TMP	94,7	76,5	78,6
Ciprofloxacin	64,7	17,6	42,9
Cefotaxim	50,4	47,1	57,1
Ceftazidime	50,4	47,1	42,9
Cefepime	50,4	44,1	42,9
ESBL confirmed	47,4	44,1	42,9
Gentamicin	54,9	29,4	35,7
Amikacin	3,8	2,9	7,1
Piperacillin/tazobactam	9,0	14,7	21,4
Meropenem	0,0	0,0	0,0
Colistin	0,8	2,9	57,1
Tigecyclin	0,0	5,9	14,3
Fosfomycin	0,0	17,6	35,7

BSI: 1/4 is *Salmonella* spp.

- Mainly *S. Choleraesuis*
  - Link with pigs, HIV patients, multi drug resistance
  - Fits in regional (East Asian) data
- Very high rates of
  - FQ resistance (ST)
  - azithromycin resistance (NTS)

Chiu, Clin Microbiol Rev 2004

Table 1. Resistance patterns of 55 *Salmonella* first isolates SHCH 2007-2010.

Antibiotic	*S.* Choleraesuis (n = 23)	*S.* Paratyphi (n = 3)	*S.* Typhi (n = 16)	other NTS (n = 13)
	% resistant isolates			
Multi drug resistance (co-resistance to ampicillin + SMX-TMP + chloramphenicol)	95,7	0,0	75,0	38,5
Fluoroquinolone resistance				
Nalidixic acid*	30,4	0,0	87,5	38,5
Decreased ciprofloxacin susceptibility (DCS)*	30,4	33,3	87,5	53,8
Second line antibiotics				
Azithromycin*	73,9	33,3	6,3	7,7
Cefotaxim**	0,0	0,0	0,0	0,0
Combined resistance				
MDR + DCS	26,1	66,7	6,3	23,1
MDR + DCS + azithromycin	13,0	0,0	0,0	7,7
Reserve antibiotics				
Meropenem	0,0	0,0	0,0	0,0
Tigecyclin	0,0	0,0	0,0	0,0
Fosfomycin	0,0	0,0	0,0	0,0
Colimycin	13,0	0,0	0,0	38,5

** breakpoints: MIC nalidixic acid ?32 mg/l; MIC ciprofloxacin > 0.06 4mg/l; MIC azithromycin >16 mg/l*

***Not included: 1 isolate S. Choleraesuis from recurrent infection, ESBL-positive*

DR Congo

Survey on 'typhoid fever', Kinshasa

- Diagnosis: Widal test + clinical
  - Only 1% of all health centres performed blood cultures!
- Widal testing:
  - EQA assesment: poor perforance
  - KAP survey: poor understanding of indications and interpretation
  - Technical aspects: many errors…
- Blood cultures: S. typhi only **2.4%** of all suspected typhoid fever

Data: Lunguya et al, submitted

Table 7. Distribution of clinically significant organisms recovered from blood cultures in patients suspected of typhoid fever and in patients suspected of other causes of bloodstream infection. Data represent numbers (%). Only the first isolate per patient was included

Organisms	Typhoid fever (3,820 patients)		Other causes (2,857 patients)		Total
	n	%	n	%	
Salmonella Typhi	92	25.3	33	9.0	125
Non typhoid Salmonella spp.	134	36.9	82	22.3	216
Klebsiella spp.	57	15.7	117	31.9	174
Escherichia coli	35	9.6	39	10.6	74
Enterobacter spp.	25	6.9	52	14.2	77
Staphylococcus aureus	20	5.5	44	12.0	67
Total	363	100	367	100	730

Data: Lunguya O. et al, submitted


RÉPUBLIQUE DÉMOCRATIQUE DU CONGO
RÉPUBLIQUE CENTRAFRICAINE
SOUDAN
CAMEROUN
CONGO
GABON
OUGANDA
RWANDA
BURUNDI
TANZANIE
ANGOLA
ZAMBIE
Bondo
Gemena
Buta
Isiro
Lisala
Bumba
Bunia
Basankusu
Kisangani
Mbandaka
Boende
Butembo
Ikela
Kivu
Goma
Inongo
Bukavu
Kindu
Bandundu
KINSHASA
Ilebo
Lusambo
Kikwit
Kananga
Mbuji-Mayi
Boma
Matadi
Tshikapa
Muanzanza
Gandajika
Mwene-Ditu
Kalemie
Manono
Pweto
Kamina
Katanga
Kolwezi
Likasi
Lubumbashi
0
300 km
Division Géographique de la Direction des Archives
du Ministère des Affaires Etrangères © 2004

BSI in DRC: Most frequent pathogens

	N	%
Salmonella spp.	188	20,7
Salmonella Typhi	141	15,5
Klebsiella pneumoniae	114	12,6
Enterobacter spp.	90	9,9
Escherichia coli	71	7,8
Serratia, *Citrobacter*, *Proteus*…	44	4,8
Candida	53	5,8
Staphylococcus aureus	48	5,3
Streptococci / Enterococci	31	3,4
Non fermentative GNR	128	14,1
Total	908	100

Most of those are < 5 years old

Antibiotiques	Salmonella Typhi N= 118		Salmonella spp. N= 145	
	n	(R %)	n	(R %)
Ampicilline*	75	(63,6)	120	(82,8)
Chloramphénicol*	85	(72,0)	110	(75,9)
Co-trimoxazole*	68	(57,6)	121	(83,4)
Cefotaxime	2	(1,6)	3	(2,1)
Gentamicine	1	(0,8)	9	(6,2)
Acide Nalidixique	6	(6,1)	7	(6,4)
Ciprofloxacine*	5	(5,1)	6	(5,4)
MDR*	35	(29,8)	110	(75,9)

MDR*: MultiDrug Resistant à l'ampicilline, au co-trimoxazole et Chloramphénicol
Ciprofloxacine*: Ciprofloxacine de sensibilité diminuée
n= Nombre de souches résistantes
N= nombre total de souches

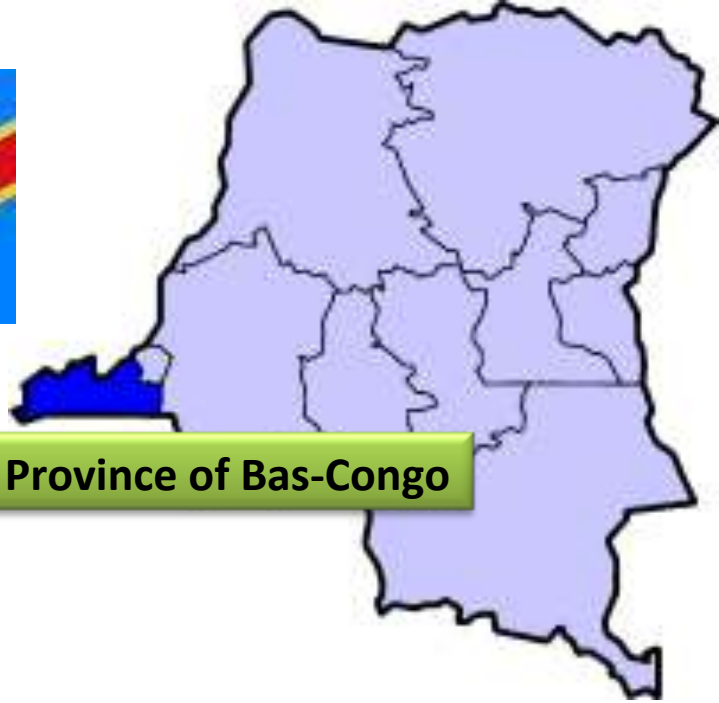
Data: Lunguya O. et al, submitted

Profil de la résistance de Klebsiella pneumoniae aux AB

Most of those are neonatal!

Antibiotiques	N = 91 n	%
Co-trimoxazole	66	74,1
Gentamicine	64	72,5
Ciprofloxacine	22	24,1
Meropenem	0	0
ESBL+	66	74,1

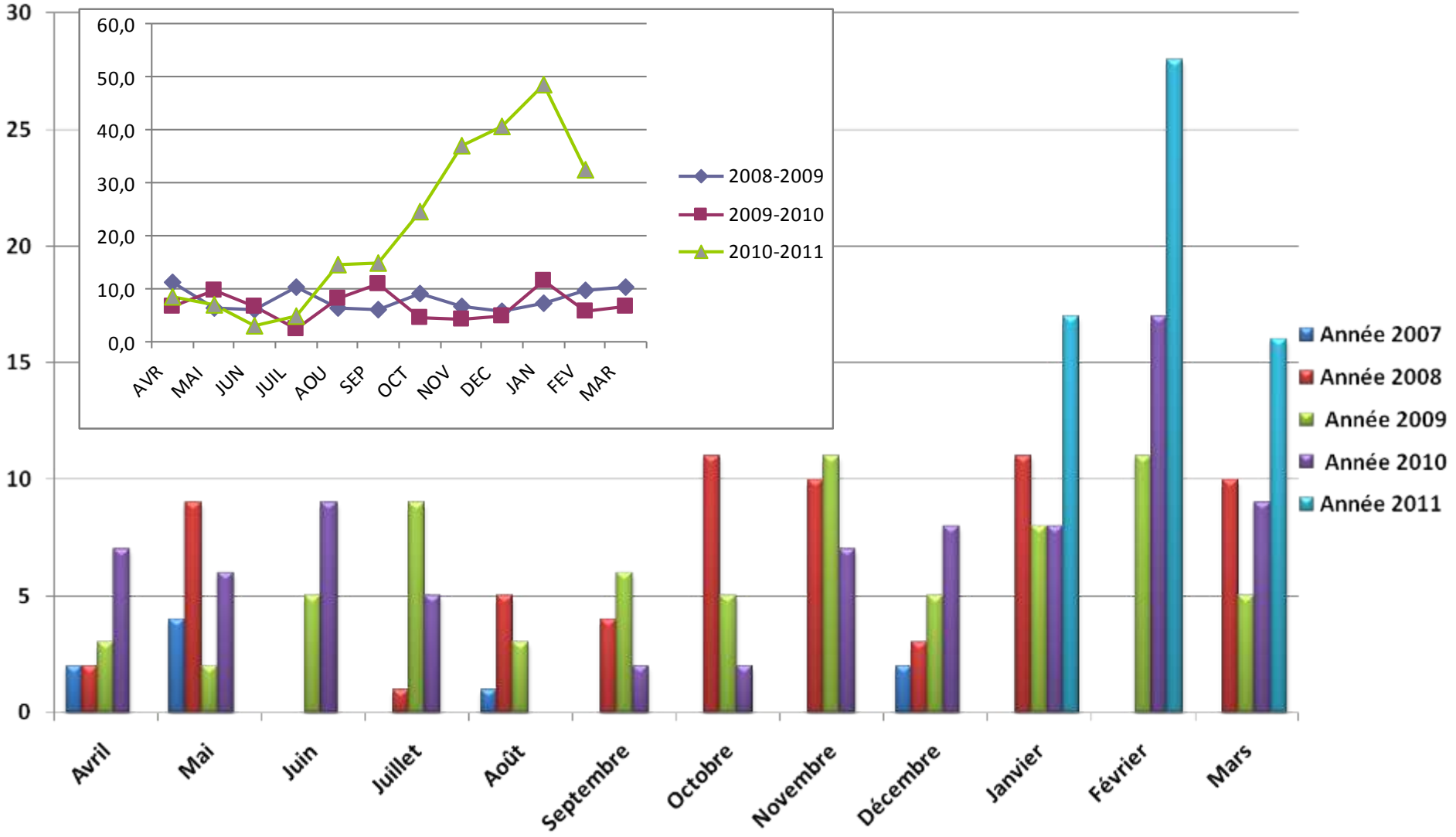
The Democratic Republic of the Congo (DRC)



Province of Bas-Congo

Hôpital Saint Luc de Kisantu (HSLK)

Increased child mortality rate made us review lab data



Increased incidence of Salmonella BSI at the HSLK …
Coinciding with the onset of rainy season

Data: Phoba, M-F et al.

Results: Isolates from BSI, September 2010 - March 2011

Serotype	Age group (years)			Total (%)
	0 - 4	5 - 9	≥ 10	
S. Enteritidis	36	6	4	46 (58.9)
S. Typhimurium	12	-	1	13 (16.7)
S. Typhi	8	-	5	13 (16.7)
Salmonella species	5	1		6 (7.7)
Total (%)	61 (78.2)	7 (9)	10 (12.8)	78 (100)

Data: Phoba, M-F et al.

Summary of findings

Increased frequency of Salmonella BSI in children < 5 yrs:

Coinciding with the onset of rainy season

High mortality rate: 25%

High antimicrobial resistance rate: > 80%

Non specific clinical presentation

Co-infection with (or co-presence of) malaria

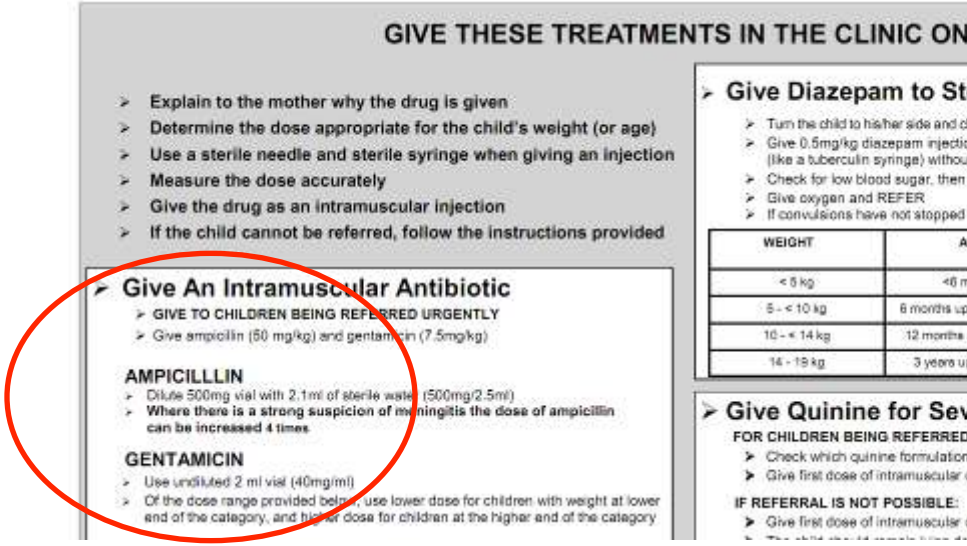
Data: Phoba, M-F et al.

High antimicrobial resistance rates to first line peroral drugs: >80%

Kenya, 2000 (Oundo): 56.3%

Tanzania, 2010 (Nadjm): 60.3%

WHO's treatment guidelines not effective for Salmonella BSI treatment http://www.who.int/child_adolescent_health/documents/imci/en/index.html


GIVE THESE TREATMENTS IN THE CLINIC ON

- Explain to the mother why the drug is given
- Determine the dose appropriate for the child's weight (or age)
- Use a sterile needle and sterile syringe when giving an injection
- Measure the dose accurately
- Give the drug as an intramuscular injection
- If the child cannot be referred, follow the instructions provided

Give An Intramuscular Antibiotic

- GIVE TO CHILDREN BEING REFERRED URGENTLY
- Give ampicillin (50 mg/kg) and gentamicin (7.5mg/kg)

AMPICILLLIN

- Dilute 500mg vial with 2.1ml of sterile water (500mg/2.5ml)
- Where there is a strong suspicion of meningitis the dose of ampicillin can be increased 4 times

GENTAMICIN

- Use undiluted 2 ml vial (40mg/ml)
- Of the dose range provided below, use lower dose for children with weight at lower end of the category, and higher dose for children at the higher end of the category

Give Diazepam to St

- Turn the child to his/her side and c
- Give 0.5mg/kg diazepam injectio (like a tuberculin syringe) withou
- Check for low blood sugar, then
- Give oxygen and REFER
- If convulsions have not stopped

WEIGHT	A
< 6 kg	<6 m
6 - < 10 kg	6 months up
10 - < 14 kg	12 months
14 - 19 kg	3 years u

Give Quinine for Sev

FOR CHILDREN BEING REFERRED

- Check which quinine formulation
- Give first dose of intramuscular

IF REFERRAL IS NOT POSSIBLE:

- Give first dose of intramuscular

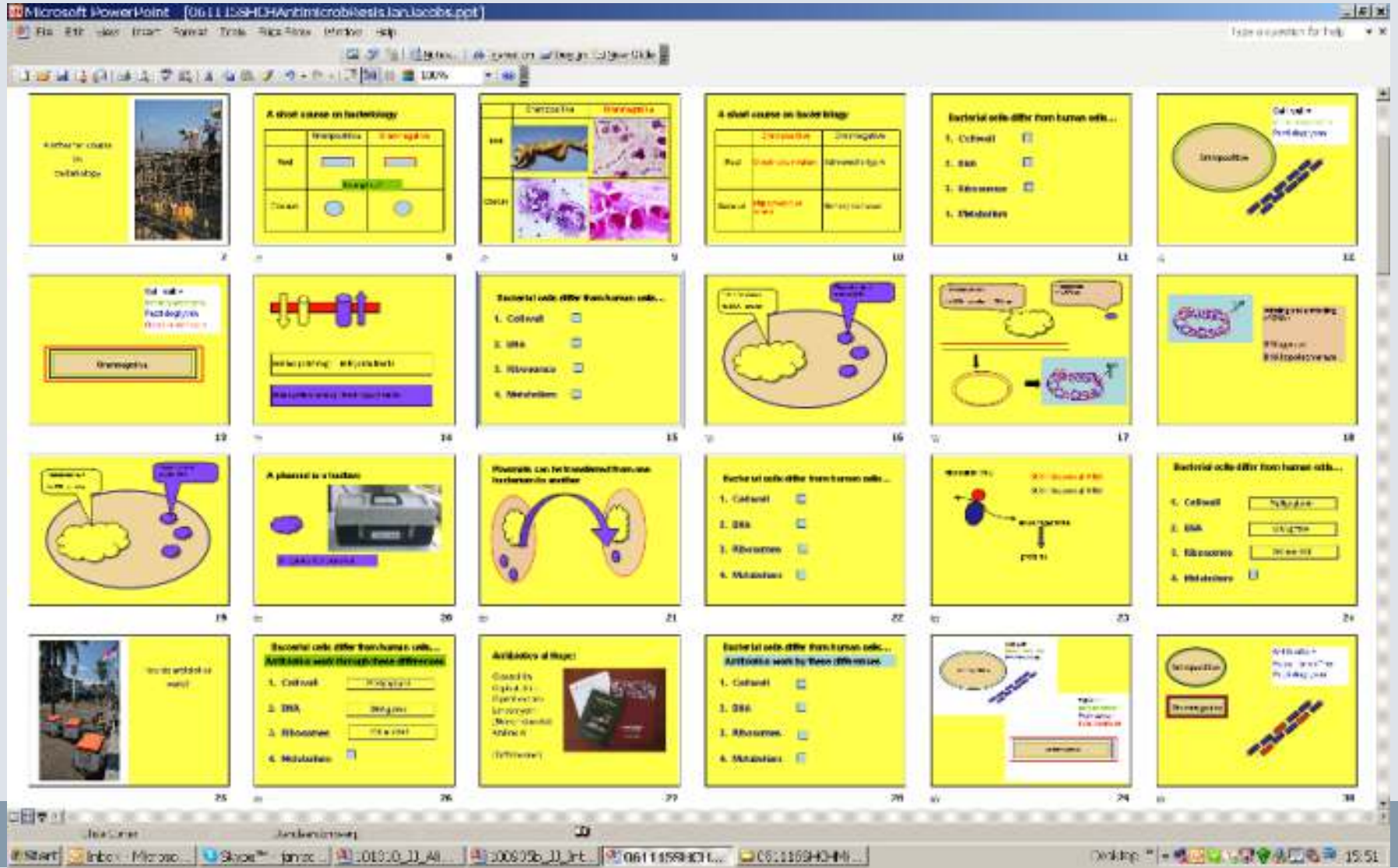
Our recommendation:

1st choice: Third generation cephalosporins

2nd choice: Fluoroquinolones

Data: Phoba, M-F et al.

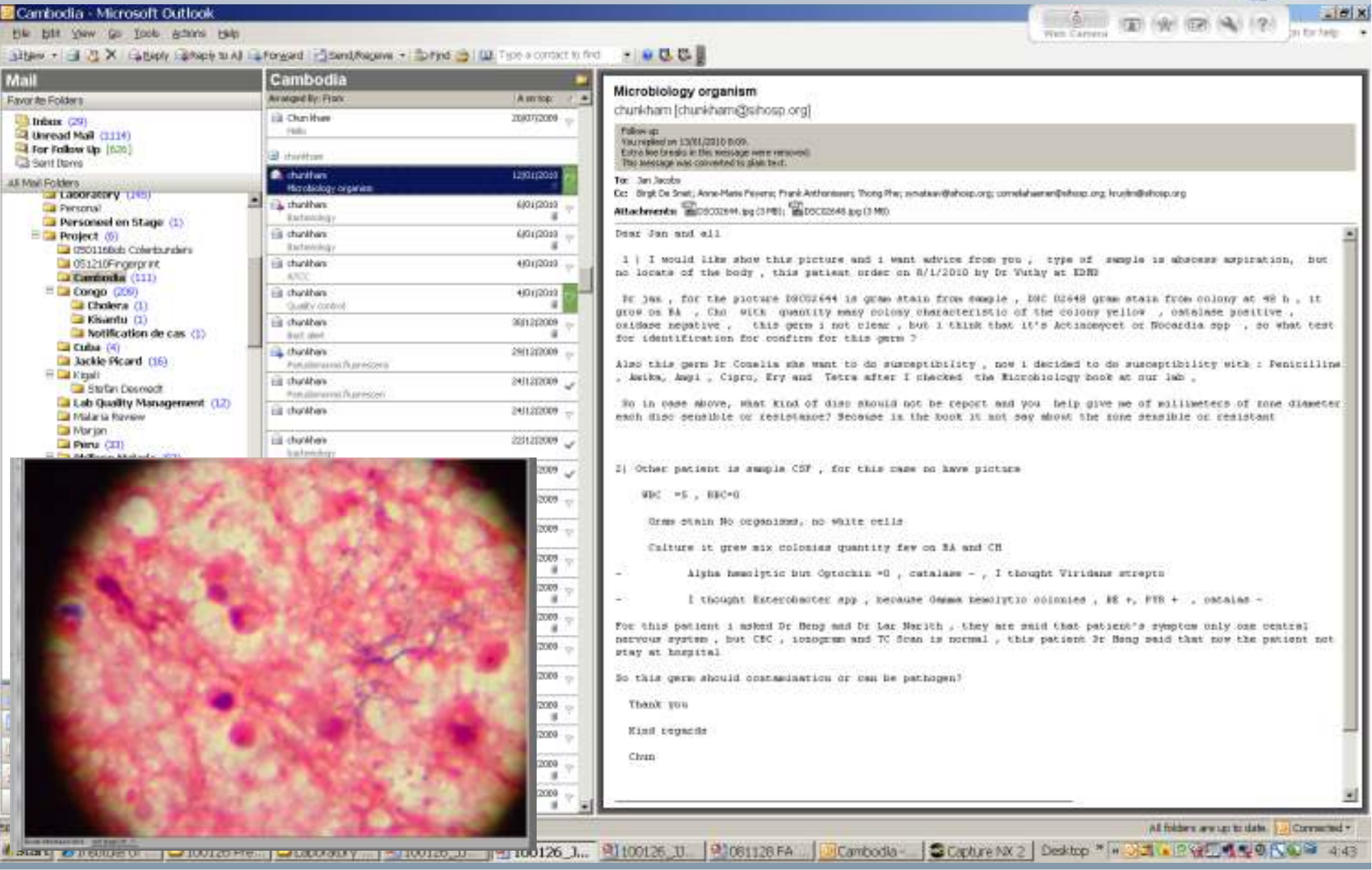
Training on “clinical” microbiology: Indications, Interpretations…



Redaction of locally adapted guidelines

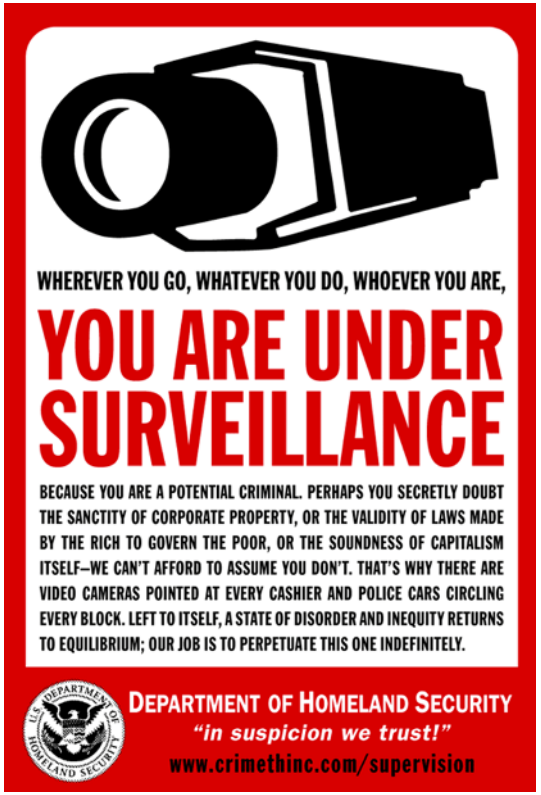
South – South trainings

Email: technical, adjunct, archive



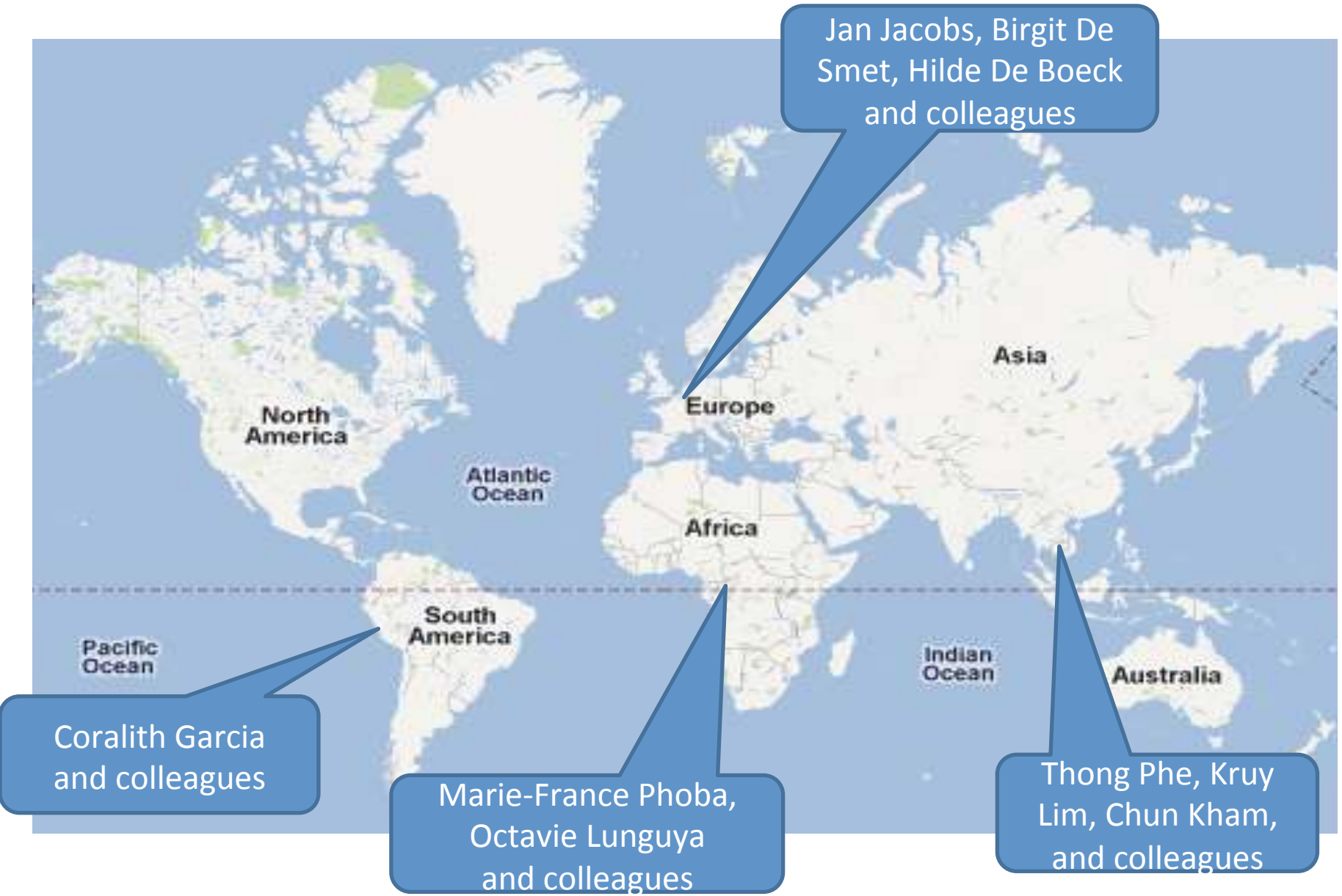
Drawbacks…

- Time & money consuming
  - ‘microbiology is not cost effective’ (or is it??)
- Bias from within
  - Patient selection
  - Geographical setting
  - Threat of commercial activities,…
- Limited n of samples, representativity,…
- Not population based, uncertain denominators
  - Incidence data…?



Very difficult things are not always impossible…

Thanks to…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Indian Ocean
Australia
Coralith Garcia and colleagues
Marie-France Phoba, Octavie Lunguya and colleagues
Thong Phe, Kruy Lim, Chun Kham, and colleagues