Ciprofloxacin and azithromycin resistance of *Campylobacter spp* isolated from international travellers, 2008-2014

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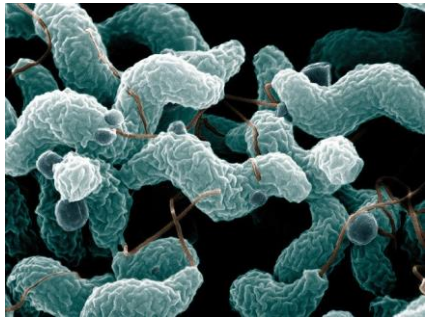
Introduction

- The speaker, Niki van Waterschoot
  - MD student at Maastricht University
  - Research internship at Institute of Tropical Medicine

- The organism *Campylobacter*
  - Frequent cause of diarrhoea
  - Increasing resistance rates



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Background

Campylobacter spp.

- Most reported zoonosis in Europe [1]
- Major bacterial cause of diarrhoea [2]

- Transmission
  - Fecal-oral
  - Person to person

- Immunocompromised patients
  - High risk (systemic) illness
  - More severe complaints

1. European Food Safety Authority, European Centre for Disease Prevention and Control. The European Union Summary Report on Trends and Sources of Zoonoses , Trends and Sources of Zoonoses , Zoonotic Agents and Food-borne Outbreaks in 2012. 2014;12(2). doi:10.2903/j.efsa.2014.3547.
2. Ross AGP, Olds GR, Cripps AW, Farrar JJ, McManus DP. Enteropathogens and chronic illness in returning travelers. *N. Engl. J. Med.* 2013;368(19):1817-25. doi:10.1056/NEJMra1207777.

Background

- Most infections are self-limited

- Antibiotic treatment is indicated when:
  - Severely dehydrated
  - High fever with bloody diarrhoea
  - Gastro-intestinal complaints >1 week
  - Systemic infection
  - High risk patients

Objectives

- Evolution of resistance
- Differences in travel regions

Trends of Norfloxacin and Erythromycin Resistance of *Campylobacter jejuni/Campylobacter coli* Isolates Recovered From International Travelers, 1994 to 2006

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Vlieghe et al.

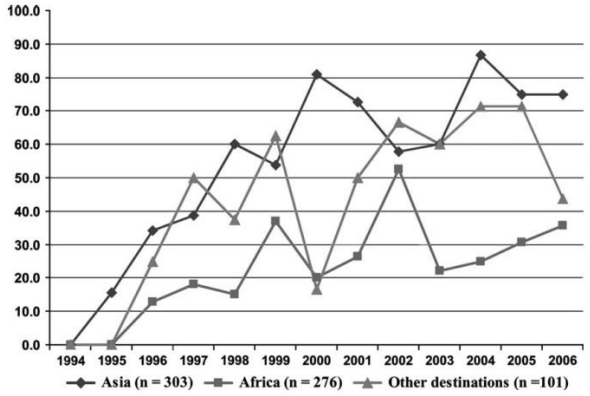
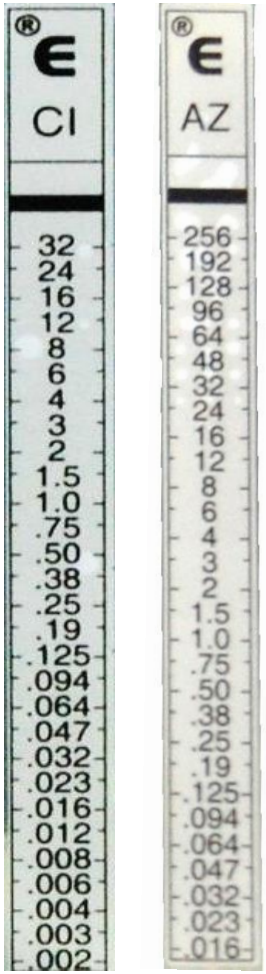


Figure 1 Annual rates of norfloxacin resistance in *Campylobacter* isolates recovered from travelers on their return from Asia, Africa, and other travel destinations (the Caribbean, Central and South America, Europe without Belgium and Australia) combined, $p < 0.001$ for the three groups.

Methods

- Period: May 2008 – November 2014
- Travel destinations were grouped according to UN composition
- MIC values determined by E-tests (bioMérieux)
- Breakpoints
  - ciprofloxacin S ≤ 1 / R ≥ 4 [1]
  - azithromycin S ≤ 2 / R ≥ 8



1. CLSI Guideline fastidious Bacteria, M45-A2, August 2010

Methods

EUCAST EUROPEAN COMMITTEE ON ANTIMICROBIAL SUSCEPTIBILITY TESTING

European Society of Clinical Microbiology and Infectious Diseases

Antimicrobial wild type distributions of microorganisms

Search

Method: (•) MIC ( ) Disk diffusion

Antimicrobial: Azithromycin Species: Species... Disk content:

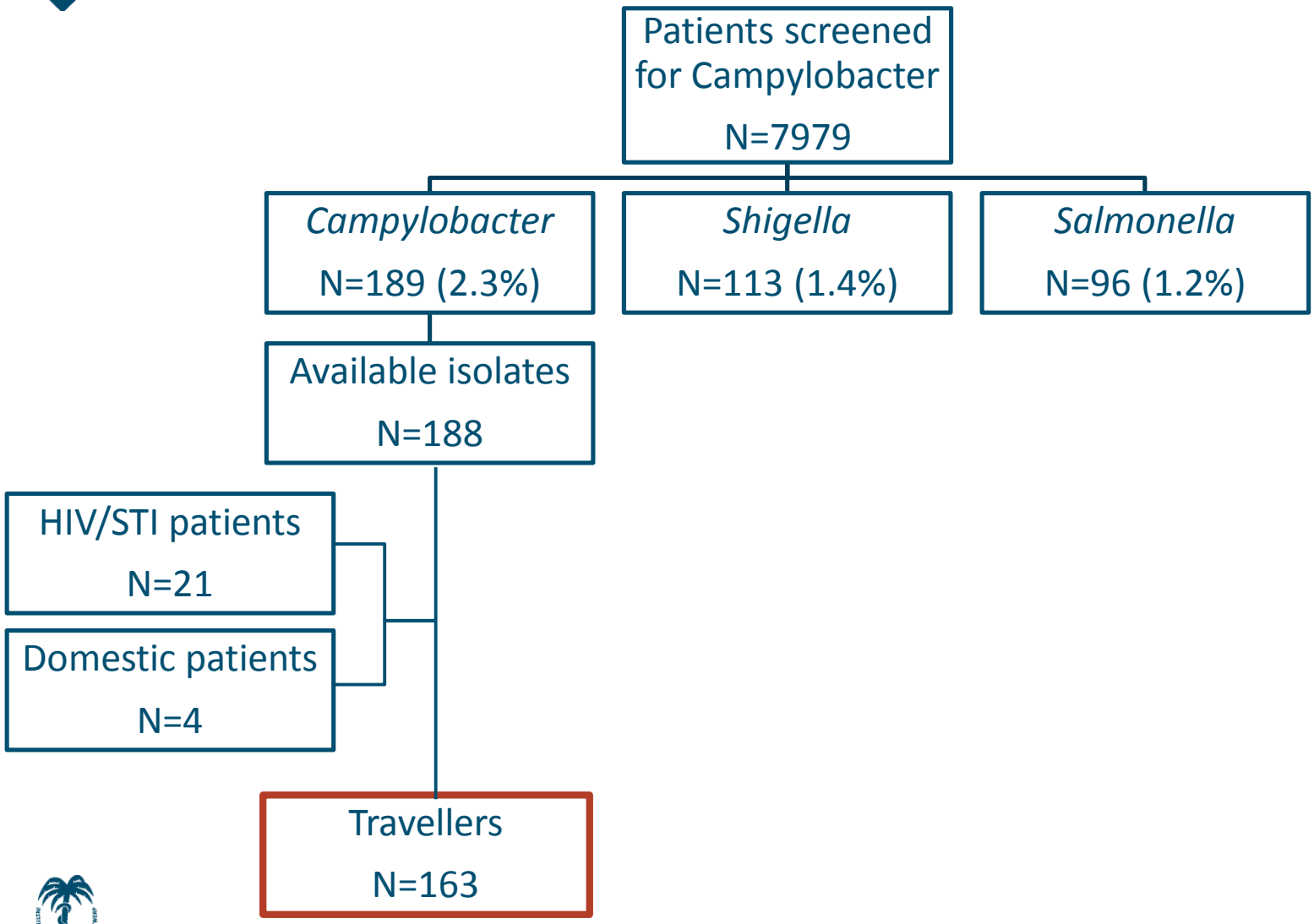
Antimicrobial: **Azithromycin** (Method: **MIC**)

MIC distributions include collated data from multiple sources, geographical areas and time periods and can never be used to infer rates of resistance

	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Campylobacter coli	0	0	0	19	350	1085	713	199	19	6	0	0	0	0	0	1	199	0	0	0.5
Campylobacter jejuni	0	0	0	507	2705	3382	1277	247	12	17	4	1	4	0	1	1	103	0	0	0.25
Legionella pneumophila	0	0	0	0	3	112	129	23	12	3	0	0	1	0	0	0	0	0	0	ND
Neisseria gonorrhoeae	0	0	4	239	401	650	967	878	403	110	34	10	17	9	3	0	0	2	0	0.25
Neisseria meningitidis	0	0	0	0	1	8	15	25	128	92	30	1	0	0	0	0	0	0	0	ND
Salmonella spp	0	0	0	0	0	0	0	0	0	1	3	159	486	75	6	2	0	0	0	ND
Salmonella typhi	0	0	0	0	0	0	0	0	0	0	9	29	89	35	3	1	0	0	0	ND
Shigella boydii	0	0	0	0	0	0	0	0	0	0	1	1	0	0	0	0	0	0	0	ND
Shigella dysenteriae	0	0	0	0	0	0	0	0	0	0	1	3	0	0	0	0	0	0	0	ND
Shigella flexneri	0	0	0	0	0	0	0	0	0	1	18	10	0	0	2	0	0	0	1	ND
Shigella sonnei	0	0	0	0	0	0	0	0	0	0	4	31	367	19	0	1	1	2	1	ND
Shigella spp	0	0	0	0	0	0	0	0	0	3	25	29	17	1	2	1	0	0	2	ND
Staphylococcus aureus	0	0	0	0	2	5	7	345	1872	1826	175	31	29	37	30	1218	1646	0	0	2.0
	0.002	0.004	0.008	0.016	0.032	0.064	0.125	0.25	0.5	1	2	4	8	16	32	64	128	256	512	ECOFF
Streptococcus pneumoniae	0	0	0	5	1248	17028	27426	1725	183	245	640	2651	3040	2596	1608	539	5541	4094	0	0.25
Streptococcus pyogenes	0	0	0	4	295	2875	15606	3360	108	44	29	117	683	456	151	50	379	186	0	0.25

Ca-

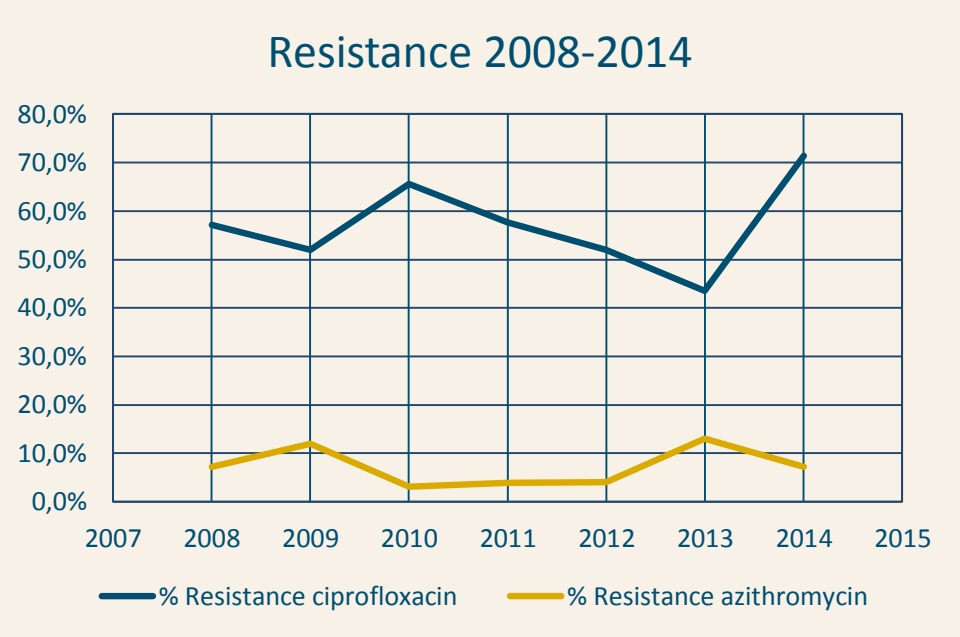
Methods


Patients screened for Campylobacter
N=7979
Campylobacter
N=189 (2.3%)
Shigella
N=113 (1.4%)
Salmonella
N=96 (1.2%)
Available isolates
N=188
HIV/STI patients
N=21
Domestic patients
N=4
Travellers
N=163

Results – Overall resistance

Ciprofloxacin resistance	
2008-2014	**57.1% (93/163)**
Lowest rate (2013)	43.5%
Highest rate: (2014)	72.2%

Azithromycin resistance	
2008-2014	**7.4% (12/163)**
Lowest rate (2010)	3.1%
Highest rate (2013)	13.0%



Results – Distribution of MIC values

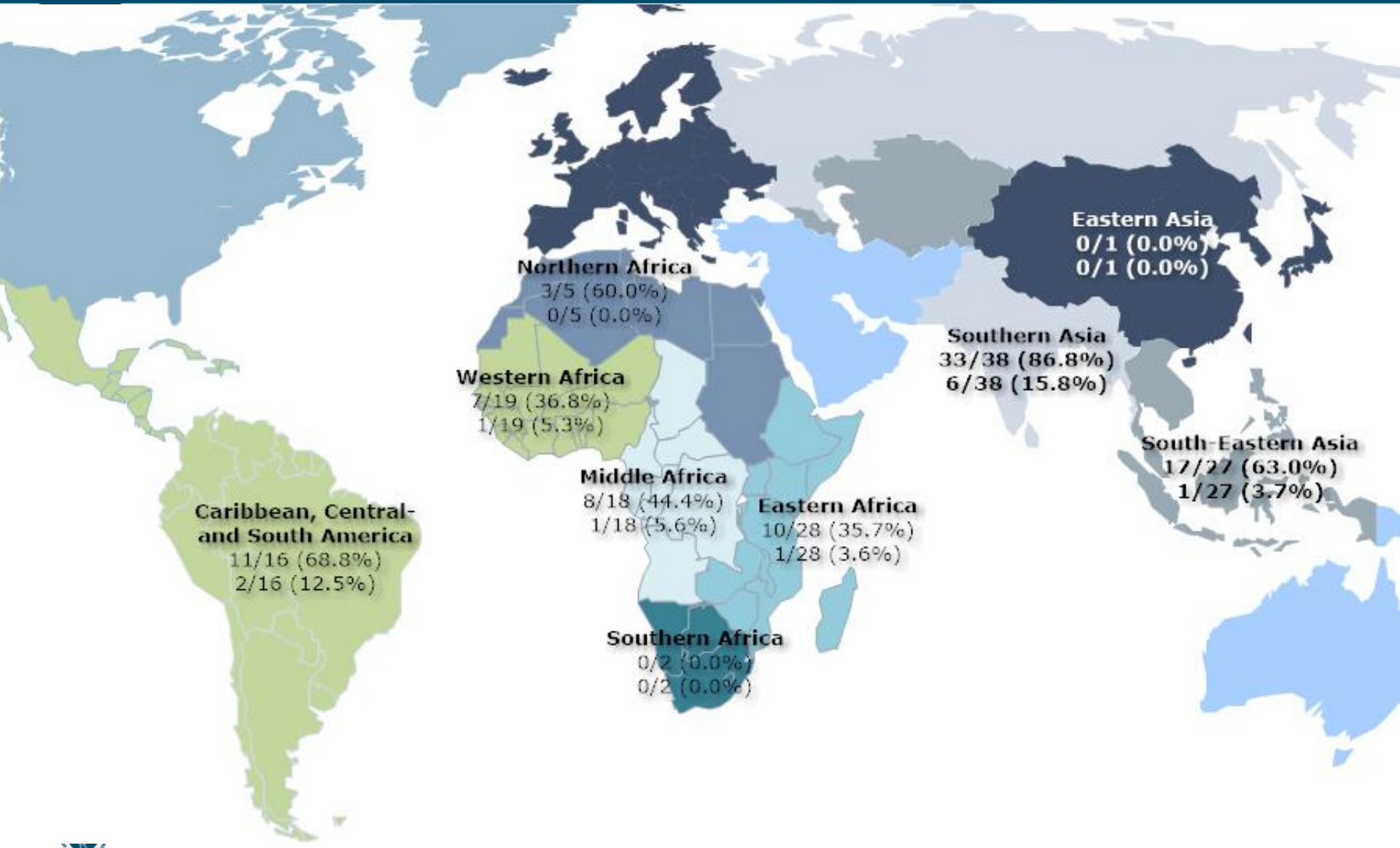
MIC Values ciprofloxacin											
mg/L	≤0,19	0,38	1,5	2	3	**4***	6	8	12	16	**>32****
N°	69	1	3	1	2	**9**	4	4	3	1	**66**
	42.3%	42.9%	44.8%	45.4%	46.6%	**52.1%**	54.6%	57.1%	58.9%	59.5%	**100.0%**

MIC Values azithromycin											
mg/L	≤0,094	**0,125***	0,19	0,25	**0,38****	0,5	1	8	12	16	>256
N°	77	**41**	13	12	**5**	1	2	1	1	1	9
	47.2%	**72.4%**	80.4%	87.7%	**90.8%**	91.4%	92.6%	93.3%	93.9%	94.5%	100.0%

* MIC 50

** MIC 90

Results – World map



Results

Region	Resistance ciprofloxacine	Resistance azithromycin
Caribbean, Central- and South America	11/16 (68.8%)	2/16 (12.5%)
Asia - Southern Asia	50/66 (75.8%)* - 33/38 (86.8%)*	7/66 (10.6%) - 6/38 (15.8%)
Africa	28/72 (38.9%)*	3/72 (4.2%)
HIV/STI	19/21 (90.5%)	4/21 (19.0%)

*P<0.05

Results – ciprofloxacin + azithromycin resistant isolates

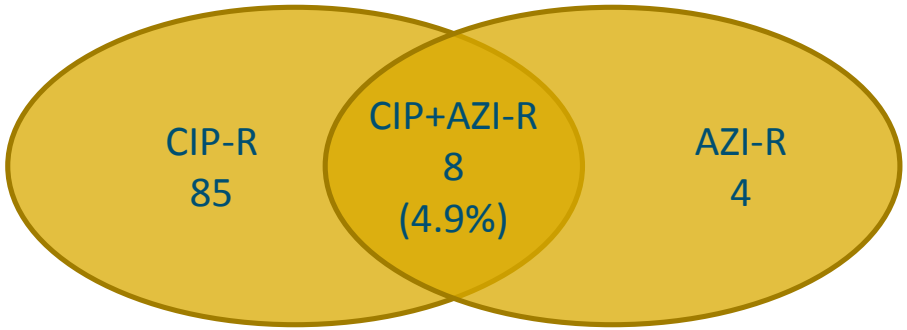


Fig 1: Ciprofloxacin and/or azithromycin resistant isolates of the study population. 70/163 CIP-S. 151/163 AZI-S

Travel destination
India
India
India
India
India
Costa Rica
Cameroon
Nepal

Discussion

- Fluoroquinolone resistance present study:
  - International travellers 2008-2014 57.1%
- Fluoroquinolone resistance earlier study:
  - International travellers 2001-2006 51.4% [1]
  - 1994-2000 25.0% [1]
- Fluoroquinolone resistance "domestic" studies:
  - United States: 2009-2011 23.0% [2]
  - The Netherlands 2010-2012 55.5% [3]
  - Belgium: 2012 62.0% [4]

1. Vlieghe ER, Jacobs J a, Van Esbroeck M, Koole O, Van Gompel A. Trends of norfloxacin and erythromycin resistance of Campylobacter jejuni/Campylobacter coli isolates recovered from international travelers, 1994 to 2006. J. Travel Med. 2008;15(6):419-25.
2. CDC Antibiotic resistance threats, United States 2013
3. Graveland H, Roest H-J, Stenvers O, et al. Staat van de Zoönosen 2012. RIVM 2013.
4. Centre National de Référence *Campylobacter,* Rapport d'activités pour l'année 2012

Discussion

- Macrolide resistance present study:
  - International travellers 2008-2014 7.4%
- Macrolide resistance earlier study:
  - International travellers 2004 7.5% [1]
  - 2006 8.6% [1]
- Macrolide resistance "domestic" studies:
  - United States: 2009-2011 2.0% [2]
  - The Netherlands 2010-2012 2.5% [3]
  - Belgium: 2012 3.0% [4]

1. Vlieghe ER, Jacobs J a, Van Esbroeck M, Koole O, Van Gompel A. Trends of norfloxacin and erythromycin resistance of Campylobacter jejuni/Campylobacter coli isolates recovered from international travelers, 1994 to 2006. J. Travel Med. 2008;15(6):419-25.
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Relevance Antibiotic treatment

- Current treatment recommendations
  - Dysentery (empirical)
    - Returning travellers – ITM Guidelines
      - From Asia → azithromycin 500mg, 1-3 days
      - Other travellers → ciprofloxacin 2dd 500mg, 3-5days
  - *Campylobacter* infection
    - Netherlands - SWAB
      - azithromycin 500mg, 3 days
    - Belgium – Sanford guide
      - azithromycin 500mg, 3 days
- Clinical correlation with *in-vitro* fluoroquinolone resistance is not straightforward

Discussion

Limitations of the study	
Retrospective	Standardised
Numbers of isolates are limited	Isolates are stored
No differentiation by reason of travel	

Future research

- Testing isolates stored 2007-2008
- Testing susceptibility other antibiotics
  - Tetracyclin
  - Amoxicillin clavulanic acid
  - Meropenem
  - (Cefixim)

Conclusion

- Findings:
  - Stable resistance rates
    - Fluoroquinolones 57.1%
    - Macrolides 7.4%
  - Marked geographical differences (Asia > Africa)
  - High level resistance among azithromycin resistant isolates
  - Confirmation: azithromycin as treatment of choice, when antibiotics are indicated

Conclusion

- Need for:
  - Continue monitoring of resistance rates (azithromycin)
  - Azithromycin treatment recommendation for diarrhoea in travellers should be extended
    - Asia
    - Caribbean, Central- and South America

- Thank you for your attention

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