asm microbe 2018
JUNE 7–11 ● ATLANTA

Atlanta – June 8th, 2018

(Room A410; 2:15-2:45)

UNIVERSITÄT BERN

Session 135:

Epidemiology of Carbapenemases: Where Are We?

Carbapenemase Producers: Epidemiology in Travelers and Community-Associated Infections

Prof. Andrea Endimiani, MD, PhD

Institute for Infectious Diseases - University of Bern, Switzerland

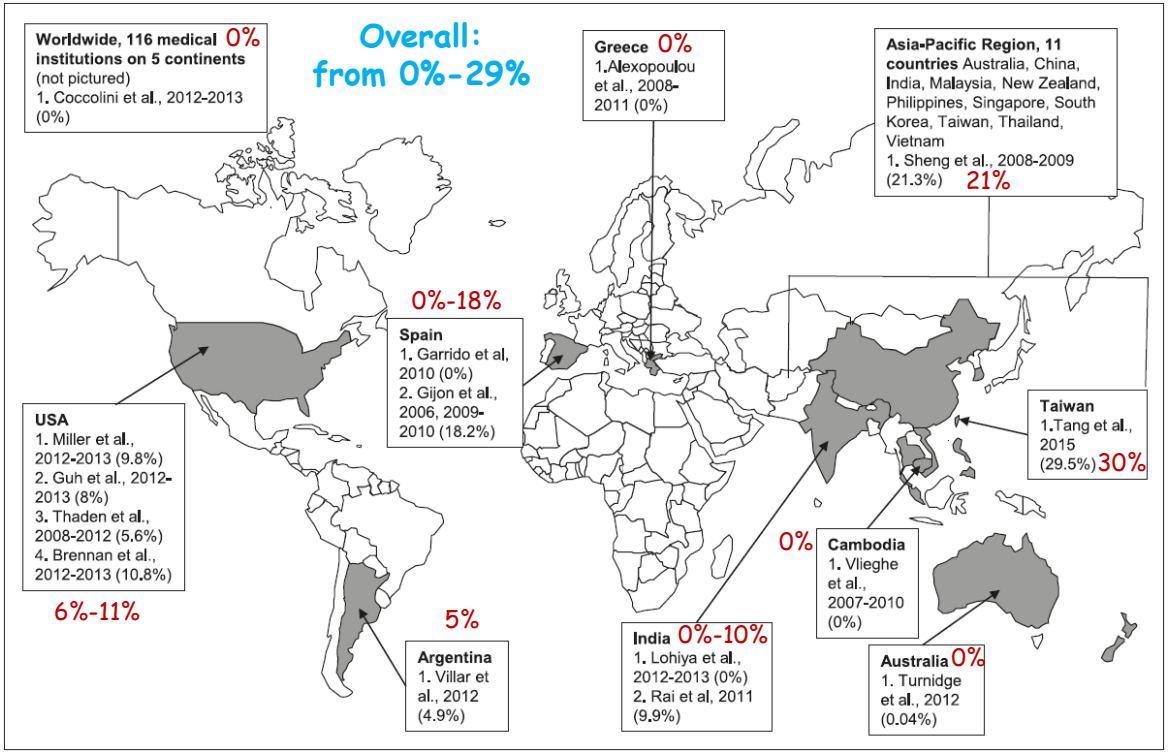
Carbapenem-resistant Enterobacteriaceae in the community: a scoping review

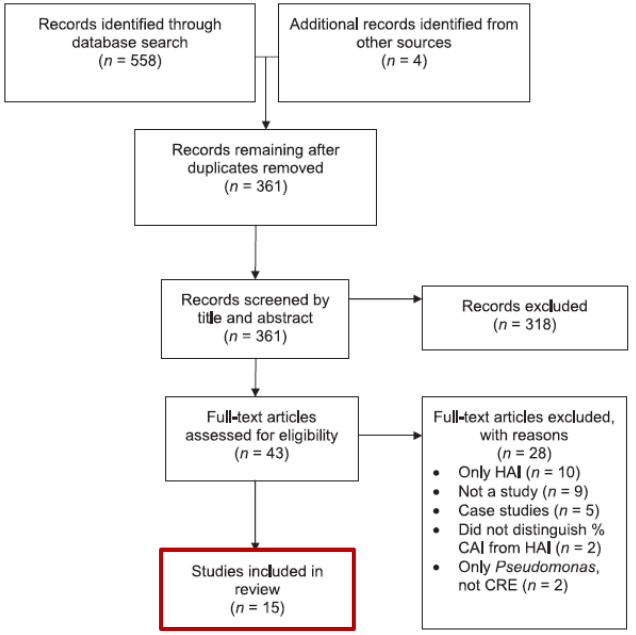
International Journal of Antimicrobial Agents 50 (2017) 127–134

Ana M. Kelly [a,*], Barun Mathema [b], Elaine L. Larson [a,b]

Literature search
1996 – March 2016

"carbapenem-resistant OR *carbapenemase* OR *carbapenem-resistant Enterobacteriaceae*
AND *community* OR *outpatient* OR *community-associated* OR *community-acquired* OR *community-onset"*





Sample sizes: 11 to 2802
(infection and colonization)

Most studies provided no/partial data about healthcare exposure

Only 4 studies performed genotypic analysis for carbapenemase genes

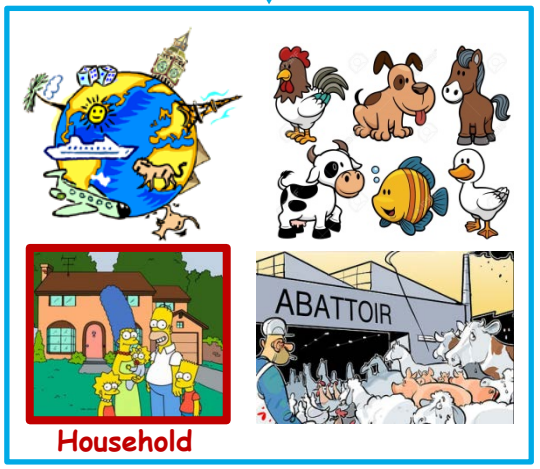
Community-Onset infection (COI)

Healthcare-associated:

- ≤ 48/72 hrs after admission
- ≥ 1 healthcare risk factors: ← If none of them "Genuine" **Community-Associated infection (CAI)**
  - hospitalization
  - surgery
  - dialysis
  - LTCF stay

  } last 12 months
  - presence of an invasive device

Infection/Colonization in the community



Study, year	Country (region)	Definition of CAI
Tang et al, 2016 [35]	Taiwan (Tainan City)	HAI if hospitalised >48 h in previous 2 weeks or residence in LTCF; all others CAI
Miller and Johnson, 2015 [36]	USA (North Carolina)	'Likely community-acquired' with no definition given, but variables on medical history collected
Guh et al, 2015 [25]	USA (7 metro areas)	'Community-associated' if no documented relevant healthcare exposure prior to positive culture
Coccolini et al, 2015 [37]	Worldwide (116 medical institutions across 5 continents)	'Community-acquired' with no definition given
Vlieghe et al, 2015 [38]	Cambodia (Phnom Penh)	'Community-acquired' if infection started before or during first 2 days of hospitalisation
Lohiya et al, 2015 [39]	India (Haryana)	No definition given, but entire sample considered 'community' because sampled healthy individuals
Thaden et al, 2014 [16] COI=60% **CAI=6%**	USA (25 community hospitals in North and South Carolina, Virginia and Georgia)	'Community acquired' if infection or colonisation occurring <48 h of patient's admission and none of the risk factors: previous hospitalisation, surgery, dialysis, or LTCF in past 12 months or presence of invasive device

2008-2012: 305 CRE

Study, year	Country (region)	Definition of CAI
Garrido et al, 2014 [40]	Spain (Zaragoza)	Infections of the 'community' were from all outpatients
Rai et al, 2014 [41]	India (East Delhi)	No definition given, but entire sample considered 'community' because attending an outpatient clinic
Brennan et al, 2014 [42] 2012-2013: 102 CRE COI=65%, **CAI=11%**	USA (Michigan)	'Community onset' if specimen was collected ≤3 days after admission, but still considered HAI if exposure to healthcare in past 90 days
Turnidge et al, 2013 [43]	Australia (all six states)	No definition given, but entire sample considered 'community-onset' because presenting as outpatients
Villar et al, 2013 [29]	Argentina (Buenos Aires)	'Community-acquired' defined by no hospitalisation in past 2 months or antibiotic use in past 7 days
Sheng et al, 2013 [44]	Asia-Pacific region (11 countries)	Presumed 'community-acquired' if organisms isolated <48 h of hospitalisation
Alexopoulou et al, 2013 [45]	Greece (Athens)	Community-acquired if present on admission or developed within first 48 h after hospitalisation
Gijón et al, 2012 [46]	Spain (Madrid)	Patients from community setting defined by samples from non-hospitalised patients, with no hospitalisation in past 3 months

Occurrence of carbapenemase-producing *Klebsiella pneumoniae* and *Escherichia coli* in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study Grundmann et al., LID, Feb 2017

Nov 2013 – Apr 2014
455 hospitals
36 countries

Klebsiella pneumoniae			*Escherichia coli*			Sentinel hospitals (mean beds†)	Incidence per 10000 admissions‡		Incidence per 100000 patient-days§	
Submitted non-susceptible isolates (n)	Confirmed carbapenemase-producing isolates* (n)	Comparator isolates (n)	Submitted non-susceptible isolates (n)	Confirmed carbapenemase producing isolates* (n)	Comparator isolates (n)		Rate (hospitals)	Rank	Rate (hospitals)	Rank
1203	850	1098	194	77	208	455 (800)	1·3 (321)	..	2·51 (268)	..
	70.6%			39.7%						

Hospitals submitting carbapenem non-susceptible *E coli* isolates (n)	Number of submitted carbapenem non-susceptible *E coli* isolates	Confirmed carbapenemase-producing *E coli* isolates					Other (n, %)*
		KPC (n, %)	NDM (n, %)	OXA-48-like	VIM (n, %)	Total (n, %)	
105	194	14 (7·2)	20 (10·3)	43 (22·2)	0	77 (39·7)	117 (60·3)
		18.2%	26.0%	55.8%			

Hospitals submitting carbapenem non-susceptible *K pneumoniae* isolates (n)	Number of submitted carbapenem non-susceptible *K pneumoniae* isolates	Confirmed carbapenemase-producing *K pneumoniae* isolates					Other (n, %)*
		KPC (n, %)	NDM (n, %)	OXA-48-like (n, %)	VIM (n, %)	Total (n, %)	
251	1203	379 (31·5)	93 (7·7)	310 (25·8)	68 (5·7)	850 (70·7)	353 (29·3)
		44.6%	10.9%	36.5%	0.08%		

RANKING

1. KPC: 42.4%
2. OXA-48-like: 38.1%
3. NDM: 12.2%
4. VIM: 7.3%

Carbapenemase-producing Enterobacteriaceae in the UK: a national study (EuSCAPE-UK) on prevalence, incidence, laboratory detection methods and infection control measures

Trepanier P et al., J Antimicrob Chemother, 2017

Isolates	*E. coli*	*K. pneumoniae*	Total
Submitted as NS to at least one carbapenem	47	55	102
Confirmed NS to at least one carbapenem	38	51	89
CPE (% of NS isolates)	7 (18)	25 (49)	32 (36)
KPC (% CPE)	0 (0)	14 (56)	14 (44)
NDM (% CPE)	2 (29)	3 (12)	5 (16)
OXA-48-like (% CPE)	5 (71)	7 (28)	12 (38)
VIM (% CPE)	0 (0)	1 (4)	1 (3)

Criteria:

HAI: inpatients > 48 hrs

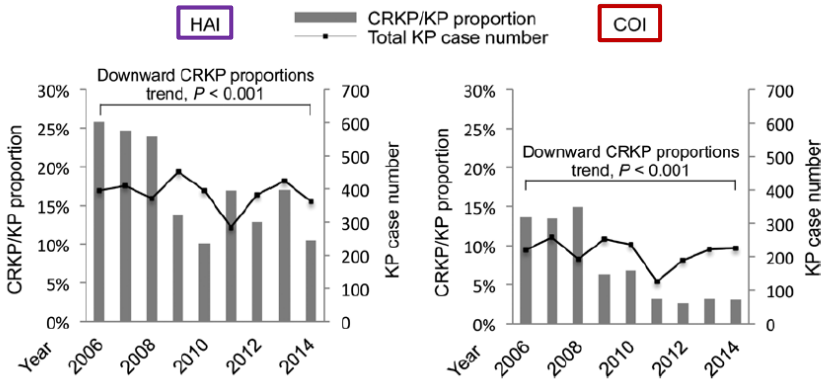
COI: outpatients or inpatients ≤48 hrs

Epidemiological characteristics	CPE (%) (*n*=32)	Non-CPE (%) (*n*=57)	Total (%) (*n*=89)
Patient characteristics			
female sex	16 (50)	40 (70)	56 (63)
mean age (standard deviation) (years)	62 (20)	59 (25)	60 (23)
Epidemiological context			
hospital acquisition	11 (34)	14 (25)	25 (28)
community onset	19 (59)	43 (75)	62 (70)
unknown	2 (6)	0 (0)	2 (2)
Hospital location			
regular ward	10 (31)	19 (33)	29 (33)
ICU	6 (19)	3 (5)	9 (10)
outpatients/emergency	14 (44)	35 (61)	49 (55)
unknown	2 (6)	0 (0)	2 (2)
Previous admission in the past 6 months			
yes	15 (47)	23 (40)	38 (43)
no	7 (22)	23 (40)	22 (25)
unknown	10 (31)	11 (19)	21 (24)
Previous travel in the past 6 months			
yes	1 (3)	1 (2)	2 (2)
no	7 (22)	11 (19)	18 (20)
unknown	24 (75)	45 (79)	69 (78)

Carbapenem-Resistant *Klebsiella pneumoniae* Infection in Three New York City Hospitals Trended Downwards From 2006 to 2014

Park SO et al., Open Forum Infect Dis, 2016

≤72 hrs
no hosp. last 30 days



Proportion of HAI and COI were positively correlated

Epidemiology of Carbapenem-Resistant Enterobacteriaceae in 7 US Communities, 2012-2013

Alice Y. Guh et al., JAMA, October 2015

Table 5. Outcome of Carbapenem-Resistant Enterobacteriaceae Cases

	No./Total (%)	
	All Cases	Case Linked to Carbapenemase-Producing Isolate
Required hospitalization at the time of or within 30 d after initial positive culture	371/569 (65.2)	65/88 (73.9)
Required intensive care unit stay in the 7 d after positive culture	128/368 (34.8)	19/65 (29.2)
Discharge disposition		
Home (private residence)	141/322 (43.8)	24/60 (40.0)
Other setting		
Long-term acute care facility or long-term acute care hospital	180/322 (55.9)	36/60 (60.0)
Inpatient hospice	1/322 (0.3)	0
Died during hospitalization or at the end of the 30-d evaluation	51/566 (9.0)	6/88 (6.8)
Among any sterile-site positive culture	25/91 (27.5)	1/15 (6.7)
Among non-sterile-site positive culture only (ie, urine specimen)	26/475 (5.5)	5/73 (6.8)

Hospital CPE are the same found in outpatients (?)

Transmission of hospital CPE to healthy people in community?

Increasing proportion of carbapenemase-producing *Enterobacteriaceae* and emergence of a MCR-1 producer through a multicentric study among hospital-based and private laboratories in Belgium from September to November 2015 Huang TD et al., Eurosurv, 2017

Species or group	2015 survey				
	Screened	CNSE	%CNSE	CPE	%CPE
24 Hospital-based laboratory					
Escherichia coli	2,560	15	0.6	3	0.12
Klebsiella pneumoniae	629	35	5.6	18	2.86
Klebsiella oxytoca	216	3	1.4	2	0.93
Citrobacter spp.	150	7	4.7	3	2.00
Enterobacter spp.	423	61	14.4	0	0
Proteaceae	551	7	1.3	0	0
Others	176	1	0.6	0	0
Total	**4,705**	**129**	**2.7**	**26**	**0.55**
10 Private community-serving laboratory[a] (serving GPs for outpatients care)					
Escherichia coli	1,276	3	0.2	1	0.08
Klebsiella pneumoniae	275	19	6.9	8	2.91
Klebsiella oxytoca	73	3	4.1	1	1.37
Citrobacter spp.	71	2	2.8	2	2.82
Enterobacter spp.	81	10	12.3	0	0
Proteaceae	184	0	0	0	0
Others	31	0	0	0	0
Total	**1,991**	**37**	**1.9**	**12**	**0.60**

Co2	Urine	Medical	*K. pneumoniae*	OXA-48	5
Co6	Respiratory	ICU	*K. pneumoniae*	OXA-48	3
Co6	Urine	Medical	*K. pneumoniae*	OXA-48	Singleton
Co7	Respiratory	ICU	*K. pneumoniae*	NDM-1	Singleton
Co8	Respiratory	Medical	*E. coli*	NDM-5, OXA-181	NA
Co8	Pus	Medical	*E. coli* [d]	OXA-48	NA
C10	Urine	Medical	*C. freundii*	OXA-48	NA
C11	Other	Other	*K. pneumoniae*	OXA-48	Singleton
C11	Urine	Other	*C. freundii*	OXA-48	NA
C12	Pus	Medical	*K. pneumoniae*	NDM-1	Singleton
C13	Urine	ICU	*K. oxytoca*	OXA-48	NA
C13	Pus	Other	*K. pneumoniae*	OXA-48	Singleton
C14	Respiratory	ICU	*K. pneumoniae*	KPC-2	Singleton
C14	Other	ICU	*K. pneumoniae*	KPC-3	Singleton
C17	Urine	Medical	*K. pneumoniae*	OXA-48	23
C17	Urine	Medical	*K. pneumoniae*	OXA-48	23
C17	Pus	Surgery	*K. pneumoniae*	OXA-48	Singleton
C17	Urine	Medical	*K. pneumoniae*	OXA-48	23
C20	Respiratory	Medical	*K. pneumoniae*	OXA-48	Singleton
C23	Urine	Medical	*K. pneumoniae*	KPC-3	16
C23	Pus	ICU	*K. pneumoniae*	KPC-2	Singleton

C26	Urine	Ambulatory	*K. pneumoniae*	OXA-48	Singleton
C26	Urine	Ambulatory	*K. oxytoca*	OXA-48	NA
C26	Urine	Ambulatory	*K. pneumoniae*	OXA-48	5
C26	Urine	Ambulatory	*K. pneumoniae*	OXA-48	5
C30	Urine	Ambulatory	*K. pneumoniae*	OXA-48	Singleton
C30	Urine	Ambulatory	*C. koseri*	OXA-48	NA
C30	Pus	Ambulatory	*K. pneumoniae*	OXA-48	3
C30	Urine	Ambulatory	*K. pneumoniae*	OXA-48	3
C30	Pus	Ambulatory	*K. pneumoniae*	OXA-48	3
C30	Urine	Ambulatory	*C. freundii*	OXA-48	NA
C33	Urine	Ambulatory	*E. coli*	OXA-48	NA
C33	Urine	Ambulatory	*K. pneumoniae*	KPC-3	Singleton

Epidemiological link between the two healthcare sectors

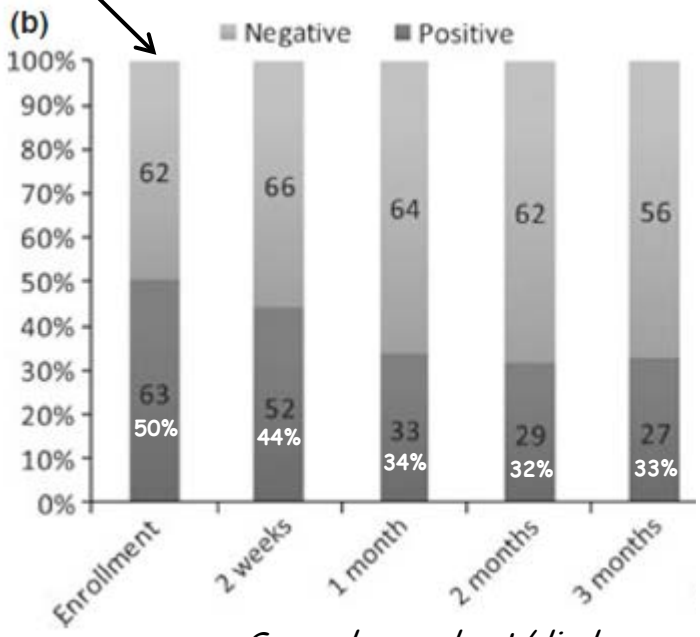
OXA-48-*Kp*: ST11, ST15, ST405, ST788
(De Laveleye et al., EJCMID, 2017)

Gastrointestinal colonization by KPC-producing *Klebsiella pneumoniae* following hospital discharge: duration of carriage and risk factors for persistent carriage

N. Feldman[1†], A. Adler[2†], N. Molshatzki[1], S. Navon-Venezia[2], E. Khabra[2], D. Cohen[1] and Y. Carmeli[2]

CMI, 2012

125 KPC-Kp carriers during hospitalization



Some dropped out/died

Before discharge

Risk factors

- Low functional status
- High Charlson index
- Invasive device
- [antibiotic use, NS]

Transmission Dynamics of Extended-Spectrum β-lactamase–Producing Enterobacteriaceae in the Tertiary Care Hospital and the Household Setting

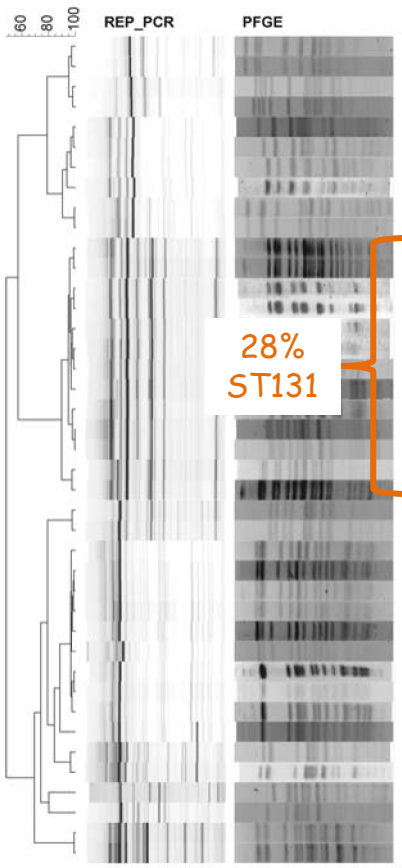
Markus Hilty,[1,a] Belinda Y. Betsch,[2,a] Katja Bögli-Stuber,[1,b] Nadja Heiniger,[1,b] Markus Stadler,[1] Marianne Küffer,[1] Andreas Kronenberg,[1] Christine Rohrer,[2] Suzanne Aebi,[1] Andrea Endimiani,[1] Sara Droz,[1] and Kathrin Mühlemann[1,2]

Clinical Infectious Diseases 2012;55(7):967–75

82 index patients (72 *Ec*; 10 *Kp*)

112 hospital contacts

96 household contacts



ID	Date of sampling	Species	Phylo. Group	pabB	ST	CTX-M	TEM	SHV	Material	Category	Age	Sex	Initial screen
164	2008-10-07	*Kp*				CTX-M-15	TEM-1	SHV-11	Faeces	HHC	0	F	
4	2008-05-16	*Kp*			147	CTX-M-15	TEM-1	SHV-11	Urine	Index	32	F	-
219	2009-12-30	*Kp*				CTX-M-15	TEM-1	SHV-2&5	Feces	HHC	66	F	
220	2009-07-14	*Kp*			15	CTX-M-15	TEM-1	SHV-2&5	Urine	Index	68	M	+
182	2009-08-04	*Ec*	D		648	CTX-M-15	TEM-1	none	Feces	HC	54	M	
199	2009-09-04	*Ec*	D			CTX-M-15	TEM-1	none	Feces	HHC	54	F	
152	2009-03-10	*Ec*	D			CTX-M-15	TEM-1	none	Feces	HHC	38	M	
67	2008-07-22	*Ec*	D			CTX-M-15	TEM-1	none	Urine	Index	43	M	+
200	2009-09-11	*Ec*	D		394	CTX-M-15	TEM-1	none	Urine	Index	57	M	+
276	2009-12-16	*Ec*	D			CTX-M-15	TEM-1	none	Feces	HHC	54	F	
55	2009-03-25	*Ec*	B2	+	131	CTX-M-15	TEM-1	none	Rectal swab	Index	80	F	+
56	2009-04-01	*Ec*	B2	+		CTX-M-15	TEM-1	none	Feces	HHC	77	M	
127	2008-08-27	*Ec*	B2	+		CTX-M-15	TEM-1	none	Feces	HHC	51	F	
128	2008-08-27	*Ec*	B2	+		CTX-M-15	TEM-1	none	Feces	HHC	24	M	
126	2008-08-17	*Ec*	B2	+		CTX-M-15	TEM-1	none	Urine	Index	52	M	+
90	2008-08-26	*Ec*	B2	+		CTX-M-15	none	none	Blood culture	Index	71	M	+
97	2009-02-25	*Ec*	B2	+		CTX-M-15	none	none	Feces	HHC	68	F	
178	2009-07-16	*Ec*	B2	+		CTX-M 27	none	none	Feces	HHC	27	F	
20	2009-06-03	*Ec*	B2	+	131	CTX-M 27	none	none	Urine	Index	1	F	-
268	2009-09-22	*Ec*	B2	+		CTX-M-15	none	none	Urine	Index	8	M	+
269	2009-11-25	*Ec*	B2	+		CTX-M-15	none	none	Feces	HHC	34	F	
168	2009-04-13	*Ec*	B2	+	131	CTX-M-15	TEM-1	none	Urine	Index	3	F	-
75	2009-04-24	*Ec*	B2	+		CTX-M-15	TEM-1	none	Feces	HHC	1	M	
203	2009-09-12	*Ec*	B2	-		CTX-M-15	TEM-1	none	Urine	Index	31	F	+
286	2009-10-02	*Ec*	B2	-		CTX-M-15	TEM-1	none	Feces	HHC	32	M	
332	2009-04-30	*Ec*	D			CTX-M-15	TEM-1	none	Feces	HHC	4	M	
133	2009-04-19	*Ec*	D			CTX-M-15	TEM-1	none	Abscess	Index	39	F	+
134	2009-04-27	*Ec*	D			CTX-M-15	TEM-1	none	Feces	HHC	2	M	
135	2009-04-27	*Ec*	D			CTX-M-15	TEM-1	none	Feces	HHC	0	F	
155	2009-04-18	*Ec*	D			CTX-M-15	TEM-1	none	Vagina swab	Index	35	F	+
225	2009-09-18	*Ec*	D			CTX-M-15	TEM-1	none	Feces	HHC	4	M	
110	2008-12-22	*Ec*	D		38	CTX-M-14	TEM-1	none	Feces	HC	64	M	-
118	2009-03-31	*Ec*	D			CTX-M-14	TEM-1	none	Feces	HHC	59	F	
70	2009-01-17	*Ec*	D			CTX-M-14	TEM-1	none	Feces	HC	71	M	
158	2009-06-02	*Ec*	D			CTX-M-14	TEM-1	none	Feces	HHC	79	F	
233	2008-10-18	*Ec*	A			CTX-M-15	TEM-1	none	Feces	HHC	70	F	
25	2008-09-24	*Ec*	A		90	CTX-M-15	TEM-1	none	Urine	Index	42	F	+
195	2009-08-31	*Ec*	A		48	none	TEM-20	none	Urine	Index	2	F	+
205	2009-09-15	*Ec*	A			none	TEM-20	none	Feces	HHC	22	F	
37	2009-05-05	*Ec*	A		23	CTX-M-1	TEM-1	none	Urine	Index	29	F	-
38	2009-05-20	*Ec*	A			CTX-M-1	TEM-1	none	Feces	HHC	34	M	

Transmission rates in hospital

- **4.5% ESBL-*E. coli***
  (5.6/1000 exposure days)
- **8.3% ESBL-*K. pneumoniae***
  (13.9/1000 exposure days)

Transmission rates at home

- **23% ESBL-*E. coli***
- **25% ESBL-*K. pneumoniae***

No studies analyzing transmission dynamics of CPE from hospital to household setting

Household Transmission of Carbapenemase-producing *Klebsiella pneumoniae*

Gottesman T et al., EID, 2008

Wife with ALS

July 2007:

hospitalized (mec. ventilation)

in Tel Aviv for 9 weeks.

Urine positive for CP-*Kp*

→ ?

73-y old man

June 2007:

TURP with no documented CP-*Kp*

Sept 2007:

routine urine positive for CP-*Kp*

OXA-48 Producing *Klebsiella pneumoniae* in a Household Contact of a Previously Infected Patient: Person-to-Person Transmission or Coincidental Community Acquisition?

Yusuf E et al., Microb Drug Res, 2016

Family member

Prostatectomy

Postoperative UTI

ST15 OXA-48-*Kp*

→ ?

18-y old woman

June 2014:

ER with UTI

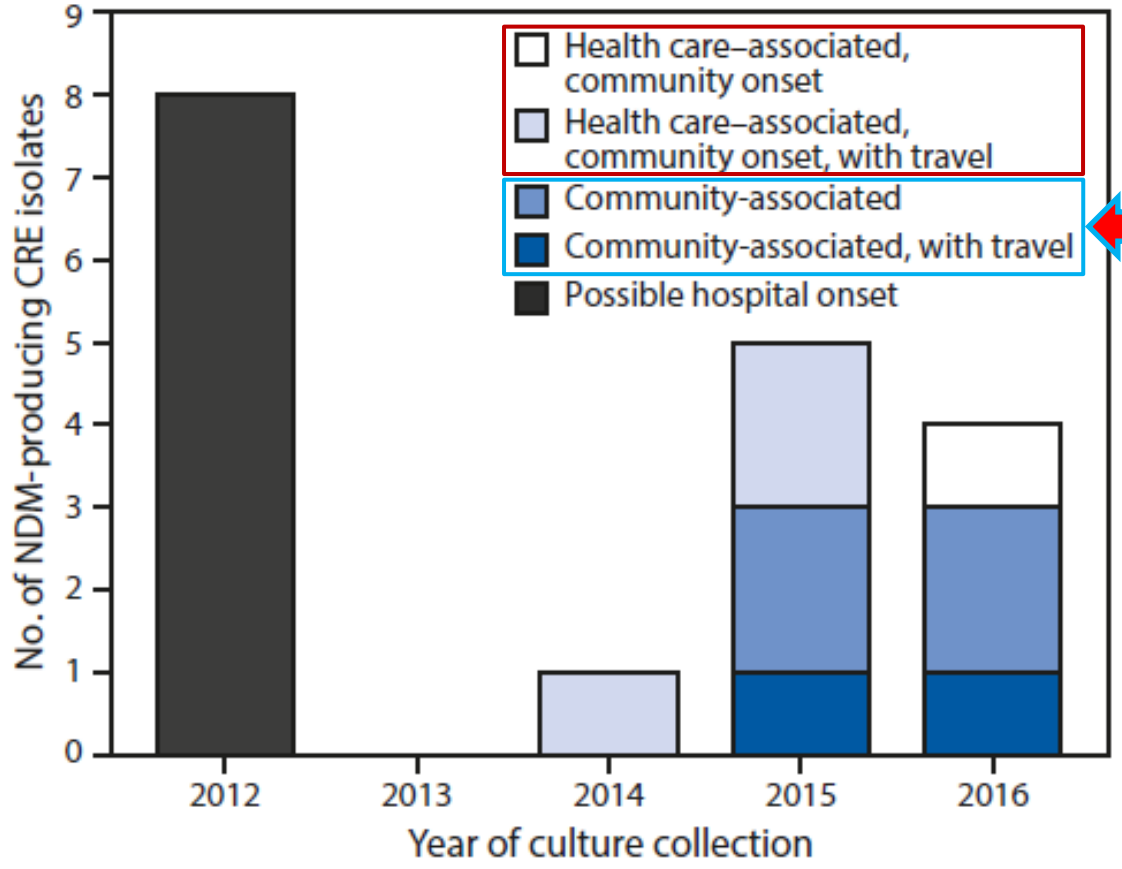
ST405 OXA-48-*Kp*

New Delhi Metallo-ß-Lactamase–Producing Carbapenem-Resistant Enterobacteriaceae Identified in Patients Without Known Health Care Risk Factors — Colorado, 2014–2016

Sarah J. Janelle, MPH[1]; Alexander Kallen, MD[2]; Tom de Man, MS[2]; Brandi Limbago, PhD[2]; Maroya Walters, PhD[2]; Alison Halpin, PhD[2]; Karen Xavier[1]; Joyce Knutsen[1]; Elizabeth Badolato[1]; Wendy M. Bamberg, MD[1]

MMWR / December 16, 2016 / Vol. 65 / No. 49

FIGURE. Number of identified CRE isolates that produce NDM, by epidemiologic classification* — Colorado, 2012–2016



1. Few studies analyzed CPE carriage in community (especially for healthy people)
2. What kind of travel and where?

Prevalence and risk factors for carriage of ESBL-producing Enterobacteriaceae in Amsterdam

Reuland EA et al., J Antimicrob Chemother, 2016

No specific screening protocol for CPE

June 2011 - Nov 2011

1,695 subjects:

healthy people referring to 5 GPs:

One OXA-48/CTX-M-14 *E. coli*

[man visiting Egypt/USA; parents from South Asia]

Extended-Spectrum-β-Lactamase-Producing *Escherichia coli* as Intestinal Colonizers in the German Community

Valenza G et al., Antimicrob Agents Chemother, 2014

No specific screening protocol for CPE

Oct 2009 - Nov 2012

3,344 subjects:

healthy people but in contact with subjects with gastroenteritis:

One OXA-244/CTX-M-14 *E. coli*

Characterization of Plasmid-Mediated β-Lactamases in Fecal Colonizing Patients in the Hospital and Community Setting in Spain

Garrido A et al., Microb Drug Res, 2014

No specific screening protocol for CPE

Jan 2010 – June 2010

2,508 subjects:

1,796 outpatients with gastroenteritis: **0%**

712 inpatients: 0%

Community carriage of ESBL-producing *Escherichia coli* is associated with strains of low pathogenicity: a Swedish nationwide study

Ny S et al., J Antimicrob Res, 2017

No specific screening protocol for CPE

Nov 2012 - Dec 2013

2,134 subjects:

People in community: **0%**

Intestinal Carriage of Carbapenemase-Producing Organisms: Current Status of Surveillance Methods

Viau R et al., Clin Microbiol Rev, 2016

Some selective plates may underestimate CPE carriage

Method	Overall sensitivity (%)	Sensitivity (%) by β-lactamase class (no. of isolates tested)			Specificity (%) (no. of negative isolates tested
		Class A	Class B	Class D	
Supercarba	95.6	100 (18)	90 (52)	100 (44)	82.2 (62)
chromID ESBL	87.7	100 (18)	98 (52)	70 (44)	24.2 (62)
CHROMagar KPC	40.3	66.7 (18)	55.8 (52)	13.6 (44)	85.5 (62)
Supercarba	96.5	100 (20)	92 (51)	100 (43)	60.7 (28)
CHROMagar KPC	43	70 (20)	58.8 (51)	11.6 (43)	67.8 (28)
Brilliance CRE	76.3	85 (20)	78.4 (51)	69.8 (43)	57.1 (28)
Brilliance CRE	86	100 (17)	72 (25)	88 (58)	40 (77)
Colorex KPC	48	100 (17)	52 (25)	31 (58)	39 (77)
Supercarba	97	100 (17)	88 (25)	100 (58)	35 (77)
Brilliance CRE	78	83 (12)	79 (103)	67 (15)	66 (70)
chromID Carba	91	100 (12)	93 (103)	67 (15)	89 (70)
chromID ESBL	96	100 (12)	98 (103)	80 (15)	19 (70)
Colorex KPC	56	83 (12)	52 (103)	60 (15)	77 (70)
CDC protocol for ertapenem	78	83 (12)	80 (103)	73 (15)	69 (70)
CDC protocol for meropenem	47	67 (12)	46 (103)	40 (15)	79 (70)
Brilliance CRE	94	100 (36)	94 (34)	84 (25)	71 (160)
mHT	100	100 (18)	ND (0)	ND (0)	96.7 (32)
RambaChrom KPC	95	95 (18)	ND (0)	ND (0)	77.1 (32)
Mero-PBA-DDST	100	100 (18)	ND (0)	ND (0)	100 (32)
Erta-PBA-DDST	100	100 (18)	ND (0)	ND (0)	91.4 (32)

No evidence so far for the dissemination of carbapenemase-producing *Enterobactericeae* in the community in Switzerland

Nüesch-Inderbinen M et al., Ant Res & Infect Control, 2013

Apr 2012 - July 2012

605 subjects:

314 healthy staffs of a meat company: **0%**

291 primary care patients: **0%**

Emergence of *Escherichia coli* producing OXA-48 β-lactamase in the community in Switzerland

Zurfluh K et al., Ant Res & Infect Control, 2015

September 2014

1,086 subjects:

healthy staffs of a meat company:

One OXA-48 *E. coli* ST38

Intestinal colonisation with extended-spectrum cephalosporin-resistant Enterobacteriaceae in different populations in Switzerland: prevalence, risk factors and molecular features

Pires J et al., J Glob Antimicrob Res, 2018

July 2013 – November 2016

337 subjects:

164 healthy staffs of VetSuisse: =**0%**

101 HIV+ subjects: **0%**

32 healthy staffs of Med Faculty: **0%**

40 healthy people not traveling: **0%**

Detection of *Escherichia coli* ST131 clonal complex (ST705) and *Klebsiella pneumoniae* ST15 among faecal carriage of extended-spectrum β-lactamase- and carbapenemase-producing *Enterobacteriaceae*

Rios E et al., J Med Microbiol, 2017

May-June 2014

501 subjects:

320 outpatients: **0%**

181 inpatients: 4.4%

[KPC-*Kp*, OXA-48-*Kp*, OXA-48-*Koxy*, VIM-*Cfr*]

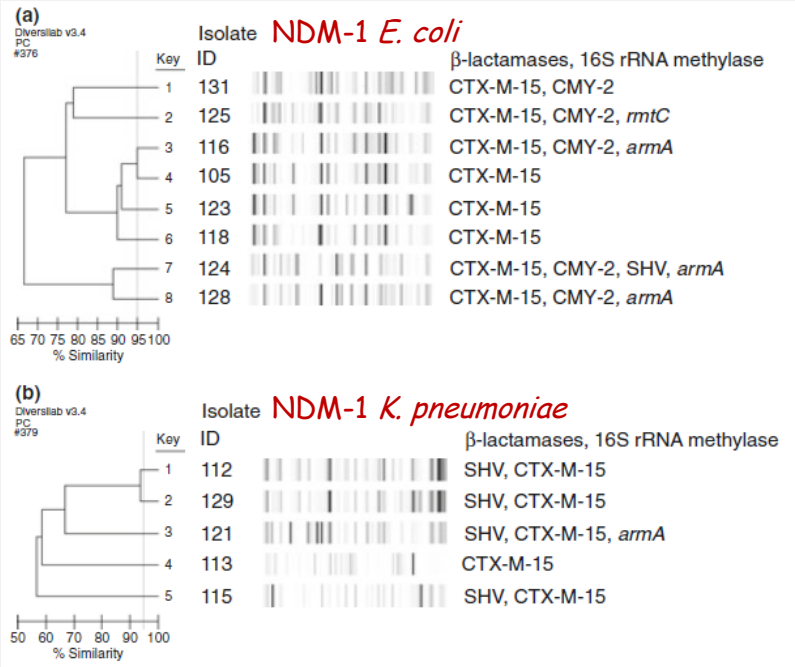
Endemic areas: people in community with diarrhea

Prevalence of NDM-1 carbapenemase in patients with diarrhoea in Pakistan and evaluation of two chromogenic culture media Day KM et al., J App Microbiol, 2017

Aug-Sept 2011

152 subjects:

people in community (≠ cities): **8.6%**



Local clusters

Fecal carriage of extended-spectrum β-lactamase- and carbapenemase-producing Enterobacteriaceae in Egyptian patients with community-onset gastrointestinal complaints: a hospital -based cross-sectional study

Abdallah HM et al., Antimicrob Resist Infect Control, 2017

No specific screening protocol for CPE

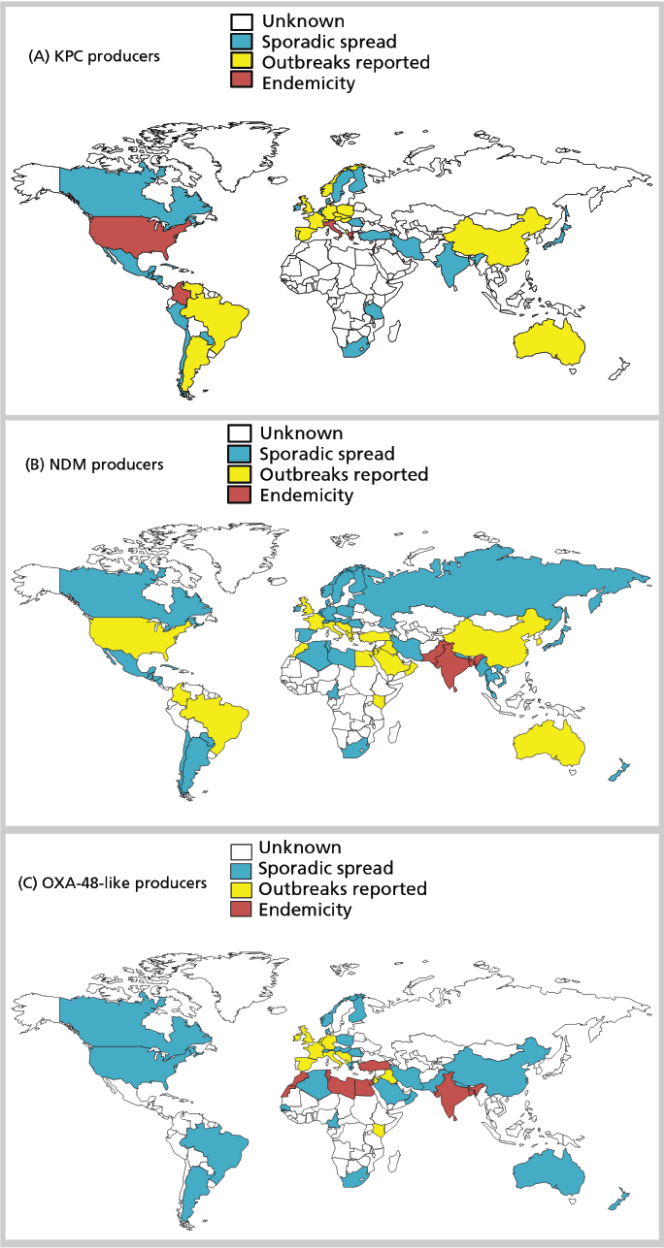
Jan-May 2013

100 subjects:

people in community: **5%**

NDM *K. pneumoniae* (n=3)

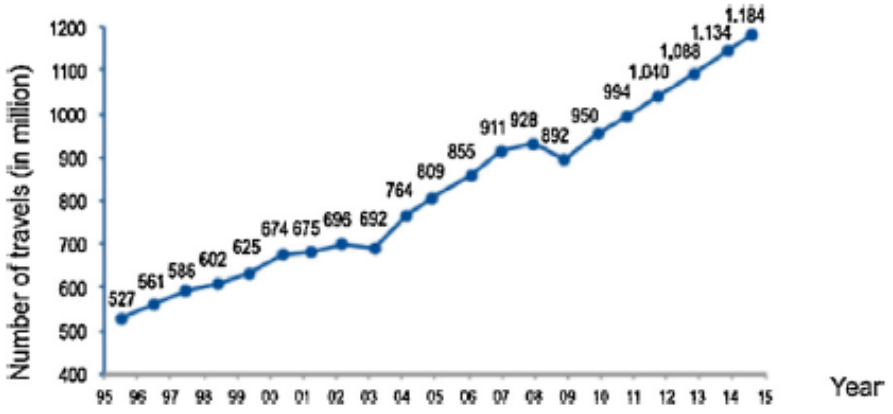
VIM *K. pneumoniae* (n=2)



R.A. Bonomo et al., Clin Infect Dis, Apr 2018

Travel and acquisition of CPE

1. **People receiving healthcare** (emergency or medical tourism)
2. **Healthy people**
3. **People with risk factors**



L. Armand-Lefèvre et al., Med Mal Infect, Feb 2018

Infection due to travel-related carbapenemase-producing *Enterobacteriaceae*, a largely underestimated phenomenon in Belgium

Jans B et al., Acta Clinica Belgica, 2015

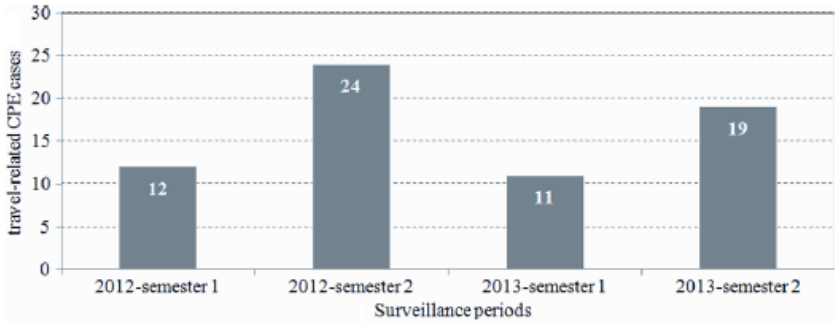
From January 2011
CNSE + epidemiological data
National Reference Center

2012-2013:

890 colonized/infected with CPE

Travel history available for 566 (64%)

66 (12%) out of 566 were travel-related (defined as "*with or without hospitalization*")



41/66 isolated at tertiary care hospitals (most in Brussels)

Africa: 29 CPE (45%)	**Asia: 18 CPE (28%)**	**Europe: 18 CPE (28%)**
Mostly OXA-48-like Nord Africa: Morocco, Tunisia, Egypt, Algeria, Senegal, Libya	**Mostly NDM** Indian subcontinent: India, Pakistan, Vietnam	**KPC and OXA-48** Turkey, Greece, Italy

The role of international travel in the worldwide spread of multiresistant Enterobacteriaceae

J Antimicrob Chemother 2012; **67**: 2090–2100

Akke K. van der Bij[1,2] and Johann D. D. Pitout[3,4]*

Receiving healthcare in endemic areas (transfer from)

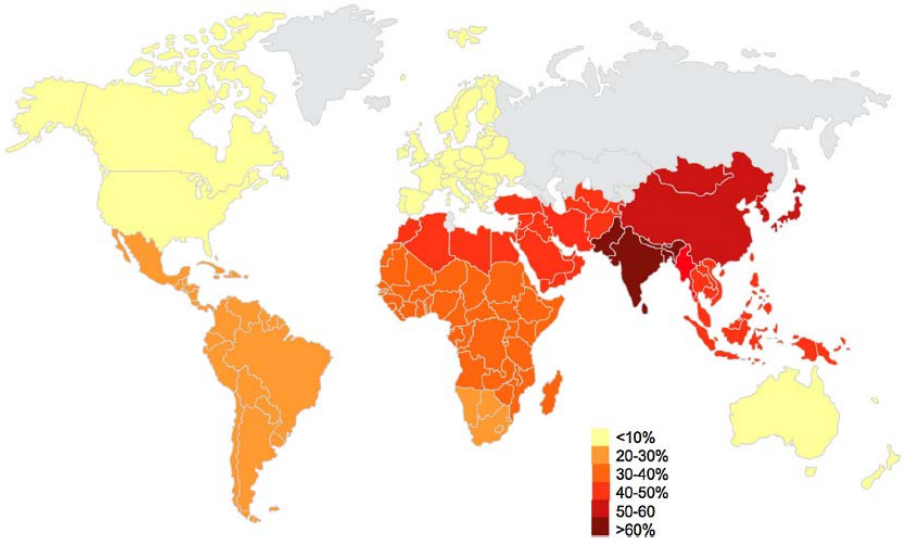
Country (year of study)	Type of study	Infections	Travellers/patients	Country visited	Organisms	β-Lactamases
France (2005)	case report	upper UTI	1	USA	*K. pneumoniae*	KPC-2
France (2005)	case report	IAI	1	USA	*E. cloacae*	KPC-3
Israel (2006)	characterization of resistance	various	100	USA	*K. pneumoniae*	KPC-3
Greece (2007)	case report	rectal colonization	1	USA	*K. pneumoniae*	KPC-2
Colombia (2008)	case reports	various	84 (32 infected)	Israel	*K. pneumoniae*	KPC-3
Norway and Sweden (2007–08)	case reports	various	7	Greece, Israel	*K. pneumoniae*	KPC-2 and -3
The Netherlands (2009)	case report	pneumonia	1	Greece	*K. pneumoniae*	KPC-2
Switzerland (2009–10)	case reports	NS	4	Greece, Italy	*K. pneumoniae*	KPC-2 and -3
Canada (2008)	case reports	UTI, IAI	3	USA	*K. pneumoniae*	KPC
UK (2009)	case report	UTI	2	Curacao	*K. pneumoniae*	KPC-2
Scandinavia (2005–08)	characterization of resistance	various	8	Greece, Turkey	*K. pneumoniae*	VIM-1
USA (2010)	case report	sepsis	1	Greece	*K. pneumoniae*	VIM
Ireland (2010)	case report	wound infection	1	Greece	*K. pneumoniae*	VIM-1
Luxembourg (2010)	case report	wound infection	1	Greece	*K. pneumoniae*	VIM-27
Sweden (2008)	case report	UTI	1	India	*K. pneumoniae*, *E. coli*	NDM-1
UK (2008–09)	characterization of resistance	various, including UTIs	37	India	*K. pneumoniae*, *E. coli*	NDM-1
The Netherlands (2009)	case reports	rectal colonization	2	India	*K. pneumoniae*	NDM-1
USA (2010)	case report	UTI	1	India	*E. coli*	NDM-1
Australia (2010)	case report	pneumonia	1	Bangladesh	*E. coli*	NDM-1
France (2010)	case report	UTI	1	India	*Citrobacter freundii*	NDM-1
Japan (2009)	case report	bacteraemia	1	India	*E. coli*	NDM-1
Germany (2009)	case report	colonization	1	India	*E. coli*	NDM-1
Austria (2009–10)	case reports	wound infection, IAI	2	Pakistan, Kosovo	*K. pneumoniae*	NDM-1
France (2010)	case report	wound infection	1	Iraq	*K. pneumoniae*	NDM-1
Canada (2010)	case report	upper UTI	1	India	*E. coli*	NDM-1
Belgium (2010)	case reports	various	3	Pakistan, Kosovo, Montenegro	*E. coli*, *K. pneumoniae*, *E. cloacae*, *Morganella morganii*	NDM-1
Singapore (2010)	case report	bacteraemia	1	Bangladesh	*E. coli*	NDM-1
France (2010)	case reports	rectal colonization	2	Morocco	*E. cloacae*	OXA-48
France (2010)	case report	rectal colonization	1	Morocco	*K. pneumoniae*	OXA-48
France (2010)	case report	endometritis	1	Turkey	*K. pneumoniae*	OXA-48
Slovenia (2011)	case report	rectal colonization	1	Libya	*K. pneumoniae*	OXA-48
Israel (2007–11)	case reports	various	4	Jordan, Georgia	*E. coli*, *K. pneumonia*, *Klebsiella oxytoca*	OXA-48

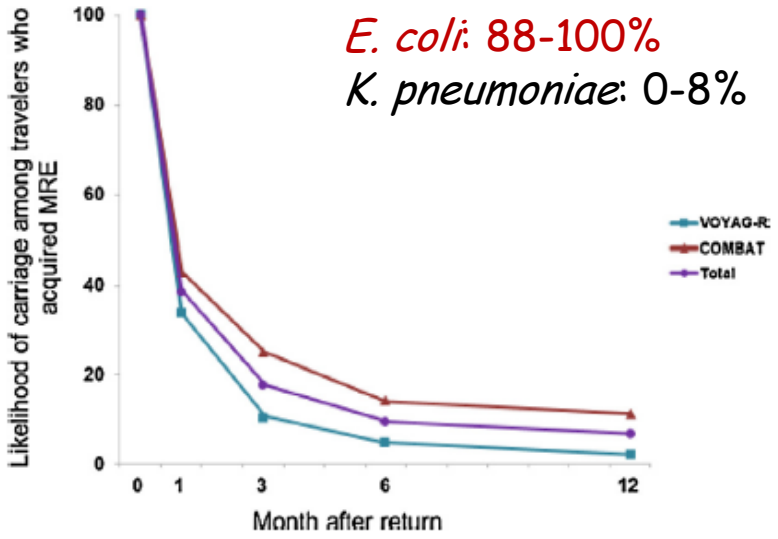
Travel and acquisition of multidrug-resistant Enterobacteriaceae

L. Armand-Lefèvre et al., Med Mal Infect, Feb 2018

Main risk factors for ESBL-*E. coli* gut carriage:

destination, digestive disorders and/or diarrhea, antibiotic intake





E. coli: 88-100%

K. pneumoniae: 0-8%

Very few studies reported acquired CPE among travelers

[most studies did not use specific protocols to detect CPE in stools]

*Maurine A Leverstein-Van Hall, James Cohen Stuart, Guido M Voets, Dik Versteeg, Thijs Tersmette, Ad C Fluit

Healthy travelers

A: 30-y man; B: 66-y woman

2009: visited India (New Delhi)

No healthcare system (HCS) exposure

Ciprofloxacin for enteritis

At return admitted to the hospital

A: urosepsis due to ESBL-*E. coli*

B: perianal abscess *Sau* + ESBL-*E. coli*

Rectal screening for A: *K. pneumoniae*

NDM-1, CTX-M-28, CMY-6, DHA-1

Rectal screening for B: *K. pneumoniae*

NDM-1, CTX-M-15

Strain A and B were unrelated

Laurent Poirel, Cécile Hombrouck-Alet, Claire Freneaux, Sandrine Bernabeu, *Patrice Nordmann

At risk person

66-y woman

2009: lives in India (Darjeeling)

No healthcare system (HCS) exposure

Brest tumor

Admitted in French Hospital

Immediate cultures from tumor surface:

NDM-1-producing *E. coli*

Colistin-R

ST131-type

Acquisition of carbapenemase-producing *Enterobacteriaceae* by healthy travellers to India, France, February 2012 to March 2013

Ruppé E et al., Eurosurv., 2014

VOYAG-R: Feb 2012 – March 2013

574 French travelers of which

57 who visited India (all negative)

0.5% CPE

5.3% India

Traveller ID	Strain	Species	Beta-lactamases	Co-resistances	Return	Follow-up		
						Month 1	Month 2	Month 3
1 (C4-049)	C4-049Ec1	*Escherichia coli*	CTX-M group 1	TE				
	C4-049Ec2	*Escherichia coli*	CTX-M group 1	FQ, SXT, TE				
	C4-049Ec3	*Escherichia coli*	CTX-M group 1	FQ, TE				
	C4-049Ec4	*Escherichia coli*	OXA-181 and CTX-M group 1	FQ				
	C4-049Ec5	*Escherichia coli*	CTX-M group 1	GM, FQ, SXT, TE				
2 (C4-417)	C4-417Ec1	*Escherichia coli*	CTX-M group 1	FQ, TE				
	C4-417Ec2	*Escherichia coli*	OXA-181	FQ				
3 (C4-422)	C4-422Ec1	*Escherichia coli*	CTX-M group 1	FQ				
	C4-422Ec2	*Escherichia coli*	CTX-M group 1 and pAmpC	GM, FQ, TE				
	C4-422Ec3	*Escherichia coli*	CTX-M group 1	FQ, TE				
	C4-422Ec4	*Escherichia coli*	CTX-M group 1	FQ, SXT, TE				
	C4-422Ec5	*Escherichia coli*	pAmpC	FQ, SXT, TE				
	C4-422Ec6	*Escherichia coli*	NDM-1 and CTX-M group 1	FQ, AN, GM, SXT, TE				

Detected

Not detected

Not provided

1:

~50-y healthy female

Traveled alone

17 days – April 2012

Backpacker tourist

No exposure to HCS or ABs

2:

~30-y healthy female

Traveled with another person

10 days – Nov 2012

No exposure to HCS or ABs

3:

~30-y healthy female

Traveled alone

30 days – Jan 2013

Backpacker + visited relatives

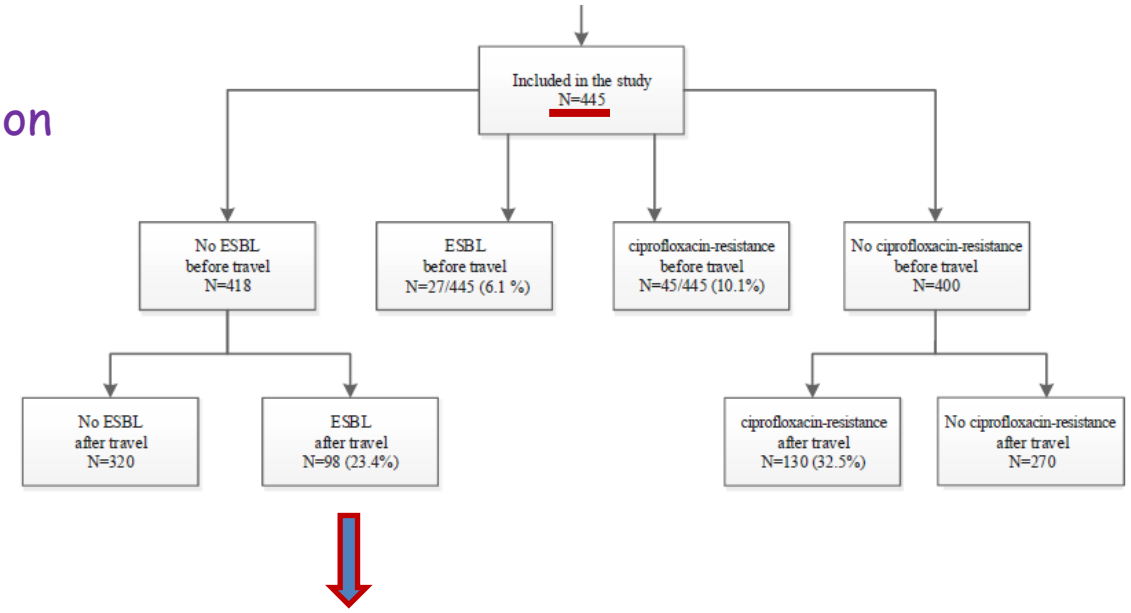
No exposure to HCS or ABs

Digestive disorders

Travel to Asia and traveller's diarrhoea with antibiotic treatment are independent risk factors for acquiring ciprofloxacin-resistant and extended spectrum β-lactamase-producing *Enterobacteriaceae*—a prospective cohort study Reuland EA et al., Clin Microbiol Infect, 2016

Vaccination Clinic, Amsterdam
Apr 2012 – Apr 2013
Africa, Asia, Latin America

No specific screening protocol for CPE detection



50-y female → **One OXA-48/CTX-M-9 *E. coli***

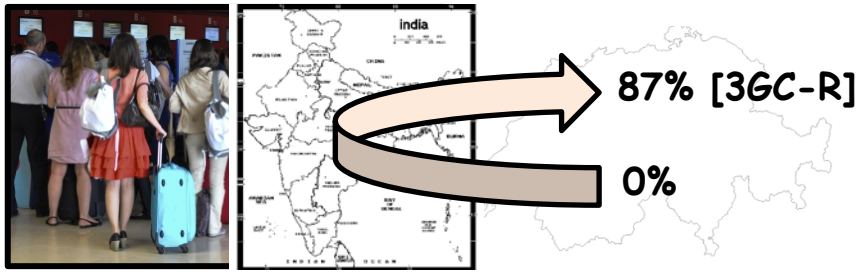
15 day visit to Egypt

No exposure to HCS or ABs

Traveler's diarrhea

High colonization rates of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* in Swiss Travellers to South Asia– a prospective observational multicentre cohort study looking at epidemiology, microbiology and risk factors

Kuenzli E et al., BMC Infect Dis, 2014



India: N=68

One CPE

NDM-1-producing *E. coli*

Overall 0.6% CPE

India 1.5% CPE

December 2012 - October 2013

170 healthy travelers negative at departure

		Univariate		Multivariate	
		OR (95% CI)	p-value[a]	adjusted OR[b] (95% CI)	p-value[a]
Destination	India	1		1	
	Bhutan	0.56 (0.13-2.40)	0.434	0.66 (0.13-3.30)	0.615
	Nepal	0.59 (0.21-1.68)	0.325	0.57 (0.17-1.88)	0.355
	Sri Lanka	0.08 (0.03-0.20)	< 0.001	0.05 (0.02-0.16)	< 0.001
Age		1.00 (0.98-1.02)	0.722		
Sex	Female	1.00			
	Male	0.99 (0.52-1.92)	0.984		
Length of Stay (per week)		1.26 (0.88-1.80)	0.215	2.08	0.010
Weight		1.01 (0.99-1.03)	0.416		
Travel Reason	Tourist	1		1	
	Business	2.07 (0.72-5.98)	0.179	1.58 (0.44-5.71)	0.483
	VFR	3.11 (1.11-8.68)	0.031	3.86 (1.02-14.59)	0.046
Sleeping Place	Hotel	1			
	Guest House	0.81 (0.40-1.64)	0.560		
	Private Household	3.35 (0.71-15.76)	0.126		
	Other	0.74 (0.16-3.36)	0.701		
Eating Place	Restaurant	1			
	Private	0.92 (0.40-2.12)	0.837		
Daily Alcohol	No	1			
	Yes	0.70 (0.34-1.45)	0.335		
Tap Water Consumption	No	1		1	
	Yes	0.52 (0.21-1.28)	0.154	0.27 (0.08-0.87)	0.029
Dairy Products	No	1			
	Yes	2.32 (0.92-5.86)	0.076		
Fruits	No	1			
	Yes	1.36 (0.51-3.67)	0.539		
Salad	No	1			
	Yes	0.59 (0.30-1.16)	0.126		
Ice Cream and Pastry	No	1		1	
	Yes	1.99 (1.03-3.85)	0.042	3.90 (1.61-9.43)	0.002
Meat	No	1			
	Yes	0.44 (0.17-1.14)	0.091		
Travellers' Diarrhoea	No	1			
	Yes	1.65 (0.81-3.33)	0.166		
PPI	No	1			
	Yes	0.88 (0.16-4.95)	0.880		

Travelers Can Import Colistin-Resistant *Enterobacteriaceae*, Including Those Possessing the Plasmid-Mediated *mcr-1* Gene

Bernasconi OJ et al., Antimicrob Agents Chemother, 2016

Polyclonal Intestinal Colonization with Extended-Spectrum Cephalosporin-Resistant Enterobacteriaceae upon Traveling to India

Pires J et al., Front Microbiol, 2016

Jan 2015 - Aug 2015

53 travelers from Switzerland to India. Follow-up at 3, 6, 12, and 24 months

No CPE carriers found

Colonization with extended-spectrum beta-lactamase-producing and carbapenemase-producing *Enterobacteriaceae* in international travelers returning to Germany

Lübbert C et al., Int J Med Micro, 2015

May 2013 - Apr 2014

225 healthy German volunteers

traveling to 53 countries

No CPE carriers found

Africa	Benin	1	**Central America and the Caribbean**	Costa Rica	2
	Botswana	3		Guatemala	1
	Cameroon	1		Kuba	3
	Congo (DR)	4		Mexiko	3
	Ethiopia	10		Nicaragua	1
	Ghana	4		Panama	5
	Ivory Coast	2		**Total**	**15**
	Kenya	18	**North America**	USA	2
	Mocambique	3			
	Namibia	3	**South America**	Argentina	5
	Seychelles	1		Bolivia	8
	South Africa	6		Brazil	15
	Swaziland	2		Chile	4
	Tanzania	17		Colombia	6
	Togo	1		Ecuador	10
	Uganda	1		Paraguay	2
	Zimbabwe	3		Peru	12
	Total	**78**		Venezuela	1
Asia	Cambodia	11		**Total**	**63**
	China	4	**Pacific**	Fiji	2
	India	15		New Zealand	2
	Indonesia	7	**Southern Europe**	France	2
	Laos	4		Italy	4
	Malaysia	8		Portugal	1
	Myanmar (Burma)	1		Turkey	1
	Nepal	2		**Total**	**8**
	Philippines	1	**Eastern Europe**	Moldova	2
	Singapore	3			
	Sri Lanka	4			
	Thailand	12			
	Vietnam	19			
	Total	**91**			

Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study

www.thelancet.com/infection Vol 17 January 2017

Maris S Arcilla*, Jarne M van Hattem*, Manon R Haverkate, Martin C J Bootsma, Perry J J van Genderen, Abraham Goorhuis, Martin P Grobusch, Astrid M Oude Lashof, Nicky Molhoek, Constance Schultsz, Ellen E Stobberingh, Henri A Verbrugh, Menno D de Jong, Damian C Melles, John Penders

Nov 2012 – Nov 2013

2001 travelers

and 168 household members

(follow up at 3, 6, 12 mo)

63 HH members (negative at base-line)

105 co-travelers (negative at return)

} who lived with travelers who acquired ESBL-E

↓

HH transmission

(criteria: same ESBL group)

←

7.7%

3/63 (4.8%)

10/105 (9.5%)

STATISTICAL MODEL:

probability of transmission = 12%

Data about the transmission of CPE acquired by travelers to household members are needed

Prolonged carriage and potential onward transmission of carbapenemase-producing Enterobacteriaceae in Dutch travelers

Van Hattem JM et al., Future Microbiol, 2016

COMBAT study

Nov 2012 – Nov 2013

2001 travelers and 215 non-traveling HH

0.25% CPE * (n=500)

All without HC exposure

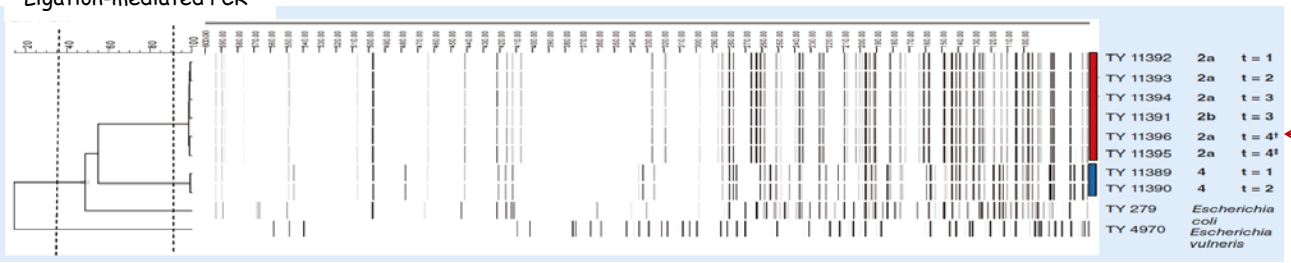
Diarrhea

Diarrhea
Antibiotic intake

Characteristics of travelers				Characteristics of journeys				Characteristics of acquired CPE			Dynamics of CPE over time					
Traveler	Age	Sex	Chronic diseases	Countries visited	Duration (days)	Period	Purpose of visit	Species	MLST	ESBL gene(s)	Before travel	On return	1 month after travel	3 months after travel	6 months after travel	12 months after travel
1	64	F	Type II diabetes	Myanmar	16	July 2013	Maritime study trip	*Enterobacter cloacae* complex	ND	None	–†	*IMI-2*†‡	–†	–†	–†	–†
2a	58	F		Indonesia	22	August 2013	Backpack holiday	*Escherichia coli*	ST38	*CTX-M-14*	–†	*OXA-244*†‡	*OXA-244*†‡	*OXA-244*†‡	*OXA-244*§¶	–§
2b	59	M	'Cardiac arrythmia'	Indonesia	22	August 2013	Backpack holiday	*E. coli*	ST38	*CTX-M-14*	–†	–†	–†	*OXA-244*†‡	–§	–§
3	41	M		Turkey, Greece	14	September 2013	Active/ backpack holiday	*Klebsiella pneumoniae*	ST363	None	–†	*OXA-48*§#	–§	–§	–§	–§
4	37	F	Asthma, hypothyro-idism	China, Thailand, Vietnam, Japan, Hong Kong and Singapore	22	October 2013	Luxury/ wellness holiday	*E. coli*	ST2914	*CTX-M-15* and *CTX-M-55*	–†	*NDM-1/2*†‡	*NDM-1/2*†‡	–†	–†	–†
5	64	F	Seborrheic eczema	Myanmar	22	October 2013	Active/ backpack holiday	*E. coli*	ST162	*CTX-M-15*	–†	*NDM-7*†‡	–†	–†	–†	–†

Possible Household Transmission

Ligation-mediated PCR



- Most of the CPE found in community are healthcare-associated
  - but in endemic areas there is probably a high prevalence of CAI/C
- Healthy travelers seem not significantly contributing to CPE importation
  - but those receiving healthcare are at high risk
- Better epidemiological data about CPE (define CAI, COI, HAI)
  - not only laboratory-based studies
- Adequate methods to screen for CPE gut carriage in community/travelers
- We need studies focusing on:
  - CPE transmission in the household (esp. from discharged patients)
  - intestinal colonization with CPE in community (healthy people)
- Better characterization of the CPE found in community/travelers (gut)

THANK YOU!

University of Bern

Institute for Infectious Diseases (IFIK)

- Odette J. Bernasconi (PhD student)
- Mathieu Clément (PhD student)
- Thomas Büdel (Lab Tech)
- Andreas Candinas (Master student)

Tropical and Public Health Institute, Basel

- Prof. Christoph Hatz
- Dr. Esther Kuenzli

Institute for Veterinary Bacteriology, Bern

- Prof. Vincent Perreten

FNSNF Swiss National Science Foundation

Grant No. 170063

72 NRP Antimicrobial Resistance National Research Programme

Grant No. 177378

Sanität

Centre of Competence for Military and Disaster Medicine, Swiss Armed Forces

Hans Sigrist Foundation (Bern)