Carriage of multiresistant bacteria after travel (COMBAT) prospective, multicentre cohort study

Perry JJ van Genderen, MD, PhD
Institute for Tropical Diseases, Harbour Hospital (now renamed to Havenpolikliniek)

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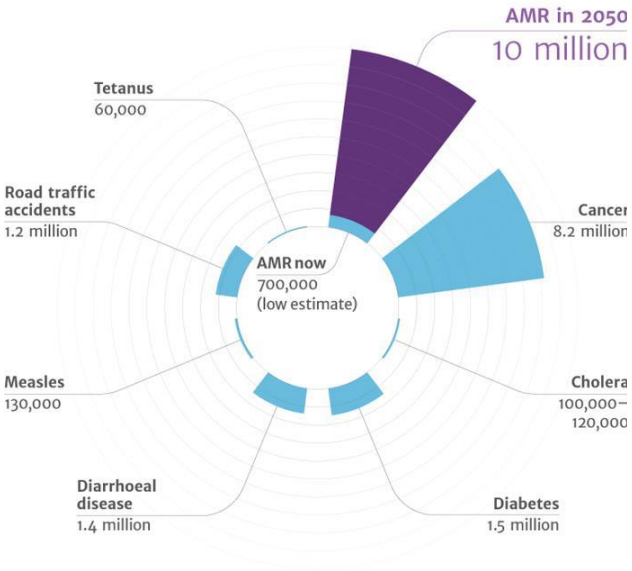
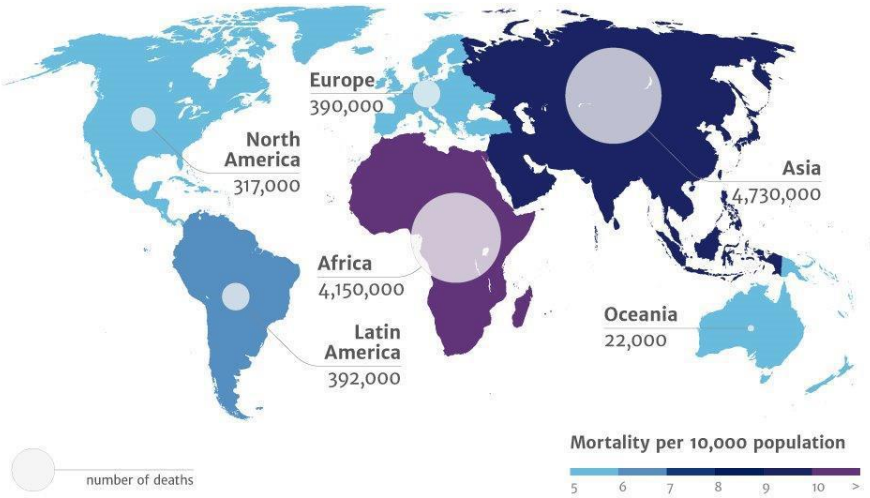
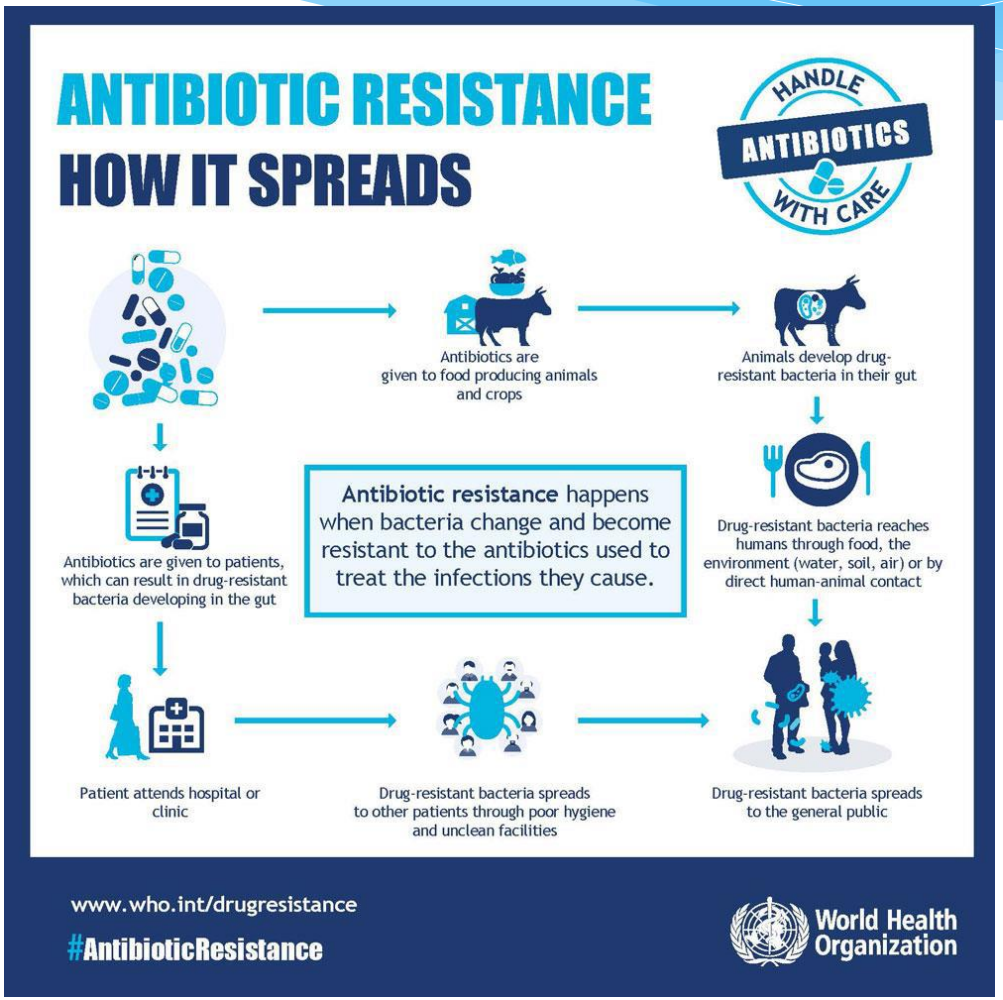
Antimicrobial resistance in 2050





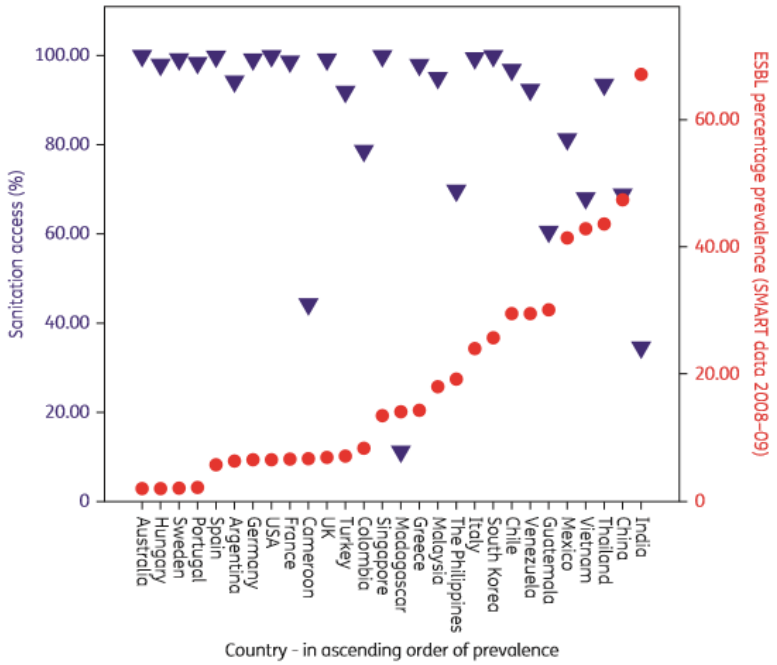
Jim O'Neill, The Review on Antimicrobial Resistance, May 2016

Antimicrobial resistance: one health approach



High prevalence of AMR in low-income countries

* Poor sanitation
* High consumption of antibiotics in humans and animals



Bevan et al., J Antimicrob Chemother 2017

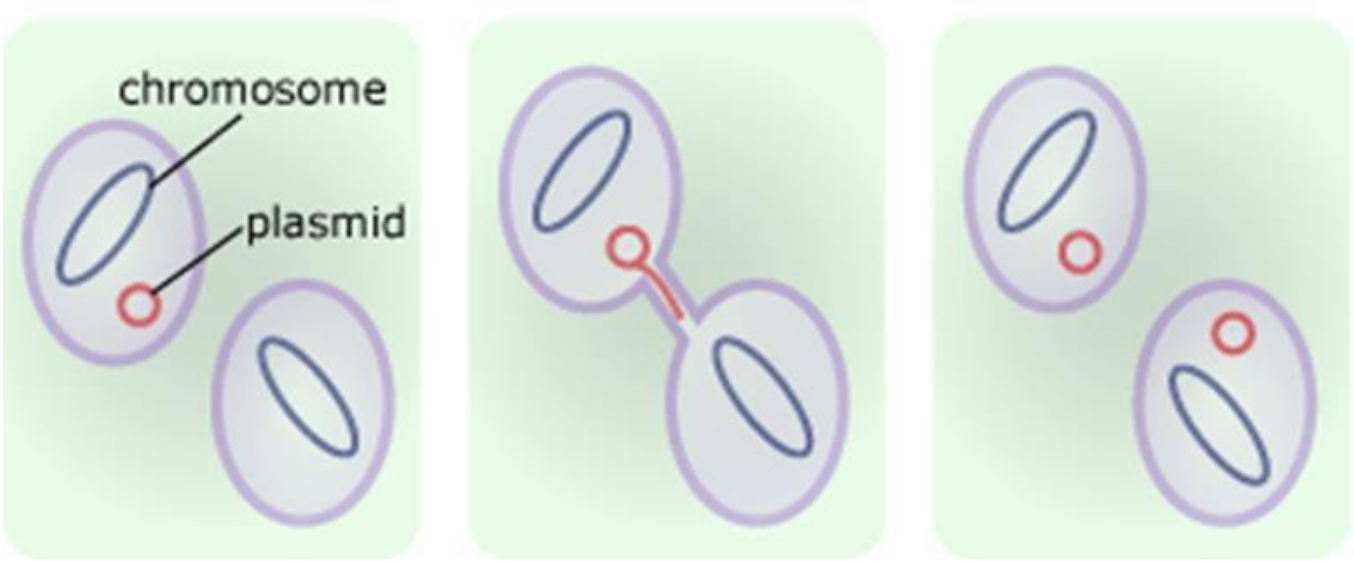
Rise of resistant Enterobacteriaceae (ESBL-E and CPE)

* **Enterobacteriaceae = Gram negative bacteria, most known *E. Coli***
  - Commensal flora gut, outside gut cause of infections (urinary tract, sepsis)
  - Treatment with beta-lactam antibiotics

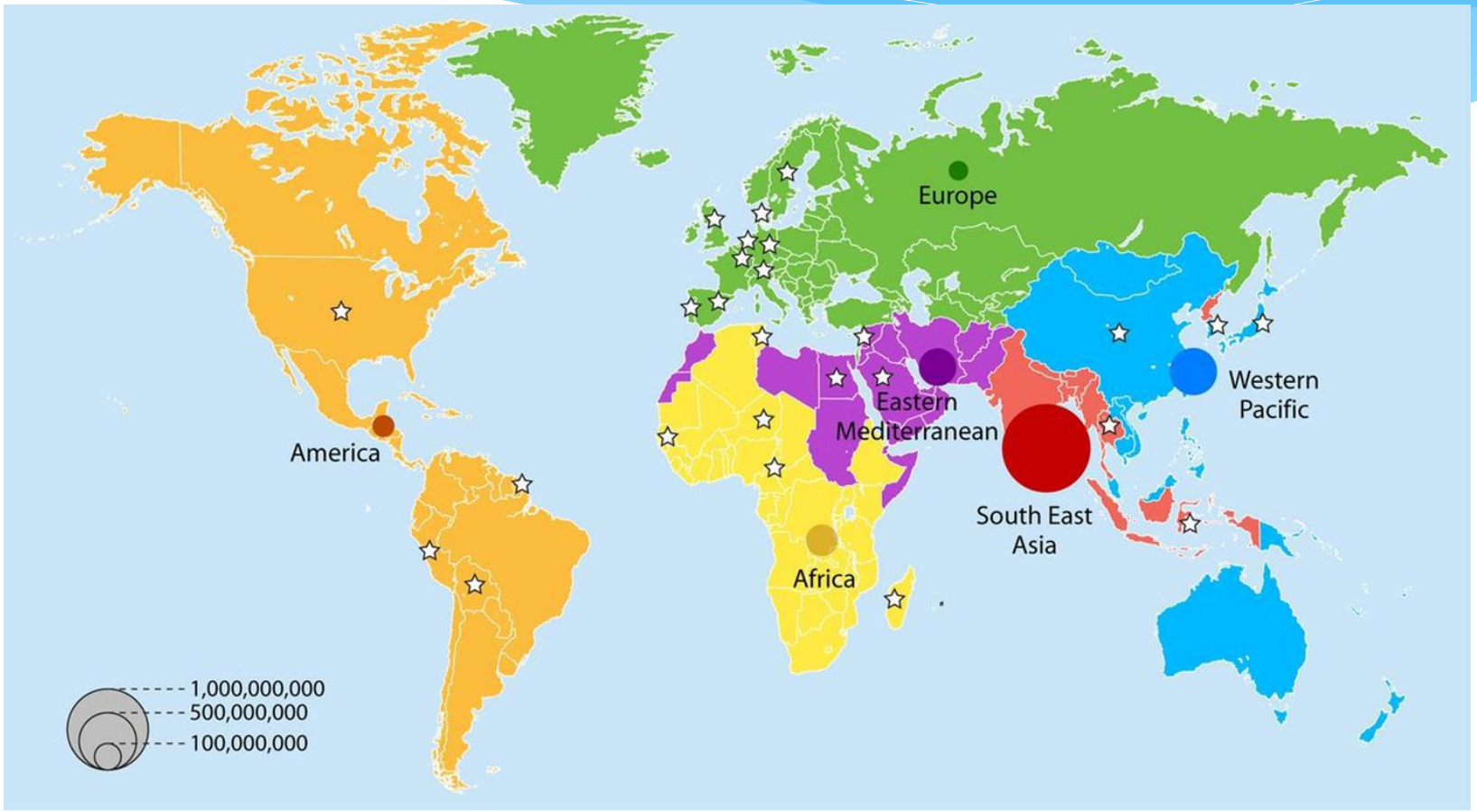
* **Rise of resistant Enterobacteriaceae**
  - Extended spectrum beta-lactamase producing Enterobacteriaceae (ESBL-E)
  - Carbapenemase producing Enterobacteriaceae (CPE)

Spread of ESBL-E and CPE

* Plasmides (= mobile genetic elements)
  - Co-resistance against quinolones, aminoglycosides and co-trimoxazol

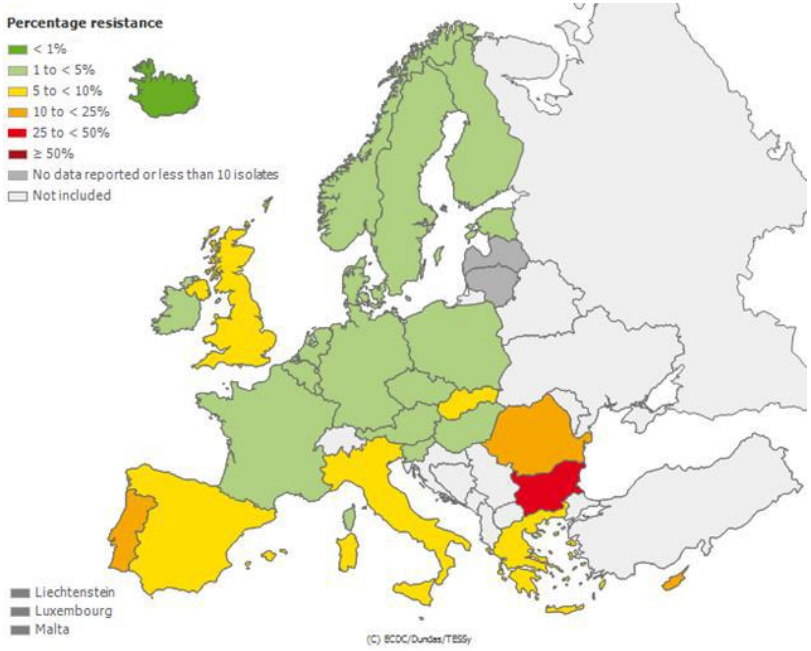


World wide spread of ESBL-E

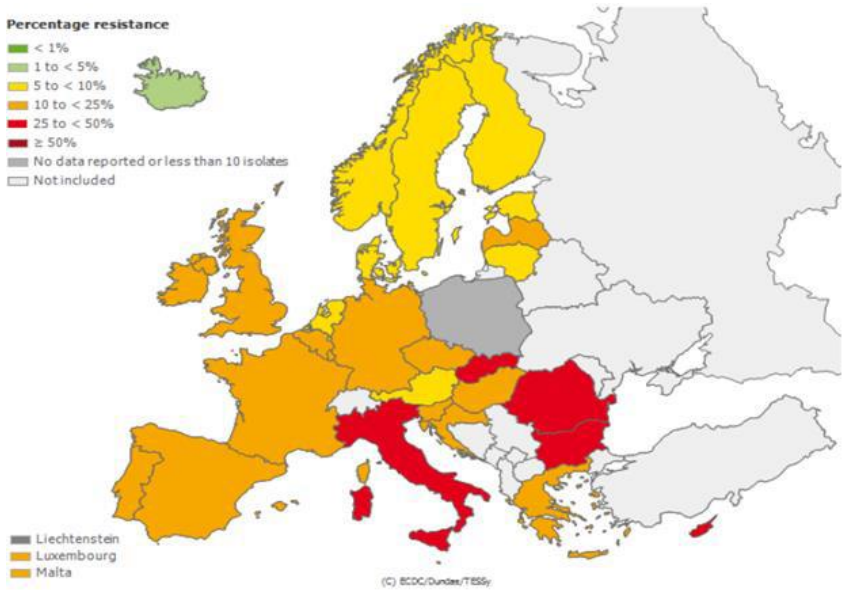


Woerther P, et al. Clin Microbiol Rev 2013

Rise of ESBL-E in Europe



2005



2014

Does increased international travel contribute to dissemination of AMR?

1,2 billion international tourist arrivals in 2016. Biggest growth in tourist to Africa, Asia and Pacific region (UNWTO Annual Report 2016)

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

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*

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See Comment page 8

*Contributed equally

Department of Medical Microbiology and Infectious Diseases, Erasmus University Medical Centre, Rotterdam, Netherlands (M S Arcilla MD, Prof H A Verbrugh PhD, D C Melles PhD); Department of Medical Microbiology, Academic Medical Centre, Amsterdam, Netherlands (J M van Hattem MD, C Schultsz PhD, Prof M D de Jong PhD); Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, Netherlands (M R Haverkate PhD, M C J Bootsma PhD); Department of Mathematics, Faculty of Science, Utrecht University, Utrecht, Netherlands (M C J Bootsma); Institute for Tropical Diseases, Havenziekenhuis, Rotterdam, Netherlands

Summary

Background International travel contributes to the dissemination of antimicrobial resistance. We investigated the acquisition of extended-spectrum β-lactamase-producing Enterobacteriaceae (ESBL-E) during international travel, with a focus on predictive factors for acquisition, duration of colonisation, and probability of onward transmission.

Methods Within the prospective, multicentre COMBAT study, 2001 Dutch travellers and 215 non-travelling household members were enrolled. Faecal samples and questionnaires on demographics, illnesses, and behaviour were collected before travel and immediately and 1, 3, 6, and 12 months after return. Samples were screened for the presence of ESBL-E. In post-travel samples, ESBL genes were sequenced and PCR with specific primers for plasmid-encoded β-lactamase enzymes TEM, SHV, and CTX-M group 1, 2, 8, 9, and 25 was used to confirm the presence of ESBL genes in follow-up samples. Multivariable regression analyses and mathematical modelling were used to identify predictors for acquisition and sustained carriage, and to determine household transmission rates. This study is registered with ClinicalTrials.gov, number NCT01676974.

Findings 633 (34·3%) of 1847 travellers who were ESBL negative before travel and had available samples after return had acquired ESBL-E during international travel (95% CI 32·1–36·5), with the highest number of acquisitions being among those who travelled to southern Asia in 136 of 181 (75·1%, 95% CI 68·4–80·9). Important predictors for acquisition of ESBL-E were antibiotic use during travel (adjusted odds ratio 2·69, 95% CI 1·79–4·05), traveller's diarrhoea that persisted after return (2·31, 1·42–3·76), and pre-existing chronic bowel disease (2·10, 1·13–3·90). The median duration of colonisation after travel was 30 days (95% CI 29–33). 65 (11·3%) of 577 remained colonised at 12 months. CTX-M enzyme group 9 ESBLs were associated with a significantly increased risk of sustained carriage (median duration 75 days, 95% CI 48–102, p=0·0001). Onward transmission was found in 13 (7·7%) of 168 household members. The probability of transmitting ESBL-E to another household member was 12% (95% CI 5–18).

Interpretation Acquisition and spread of ESBL-E during and after international travel was substantial and worrisome. Travellers to areas with a high risk of ESBL-E acquisition should be viewed as potential carriers of ESBL-E for up to 12 months after return.

Funding Netherlands Organisation for Health Research and Development (ZonMw).

COMBAT STUDY

* Determine acquisition rate of multiresistant Enterobacteriaceae during foreign travel
* Ascertain the duration of carriage of these micro-organisms
* Determine the acquisition rate within households
* Identify risk factors for acquisition, persistence of carriage and transmission of multiresistant Enterobacteriaceae

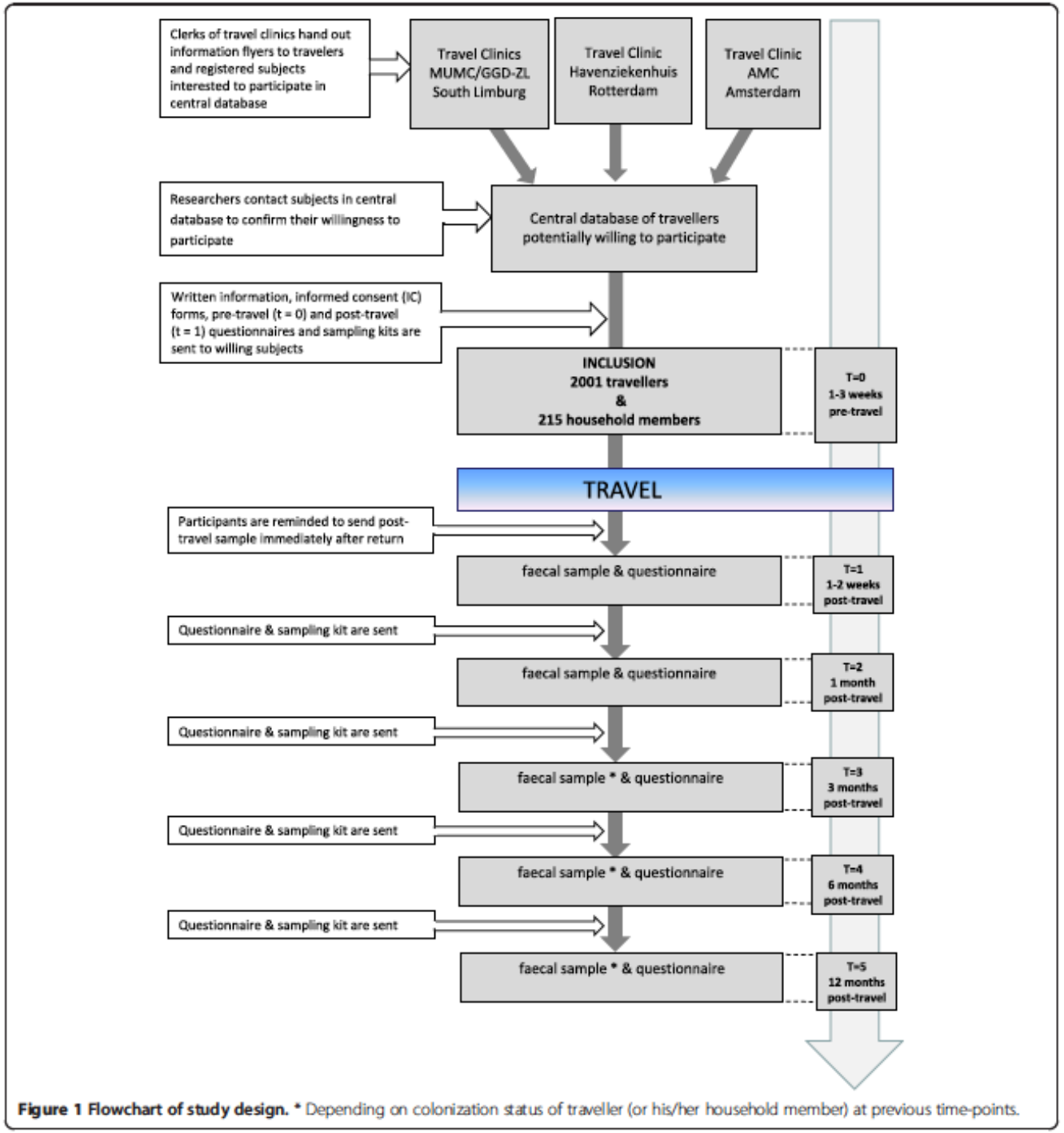


Figure 1 Flowchart of study design. * Depending on colonization status of traveller (or his/her household member) at previous time-points.

Table 1 Effect sizes that minimally can be detected according to the prevalence of the exposure in the final cohort of 2001 travellers

Proportion exposed (%)	Odds ratio
50%	1.36
25%	1.41
10%	1.64
5%	1.92

Table 2 Baseline characteristics of travellers and non-travelling household members according to study center

	Rotterdam		Amsterdam		Maastricht		Total	
	Travellers	Household members	Travellers	Household members	Travellers	Household members	Travellers	Household members
	(n = 1110)	(n = 129)	(n = 496)	(n = 43)	(n = 395)	(n = 43)	(n = 2001)	(n = 215)
Sex								
Male	541 (48.7%)	39 (30.2%)	208 (41.9%)	18 (41.9%)	171 (43.3%)	23 (53.5%)	920 (46.0%)	80 (37.2%)
Female	569 (51.3%)	90 (69.8%)	288 (58.1%)	25 (58.1%)	224 (56.7%)	20 (46.5%)	1081 (54.0%)	135 (62.8%)
Age in years (median, range)	52.0 (18.1-81.7)	46.3 (18.4-82.0)	44.7 (19.8-74.6)	41.1 (18.9-78.0)	50.4 (18.2-71.9)	50.6 (18.4-71.6)	50.5 (18.1-81.7)	46.9 (18.4-82.0)
Continents visited by traveller								
Asia	557 (50.2%)		259 (52.2%)		200 (50.6%)		1016 (50.8%)	
Africa	362 (32.6%)		148 (29.8%)		123 (31.1%)		633 (31.6%)	
America	177 (15.9%)		81 (16.3%)		68 (17.2%)		326 (16.3%)	
Europe	11 (1.0%)		6 (1.2%)		4 (1.0%)		21 (1.0%)	
Oceania	3 (0.3%)		2 (0.4%)		0 (0.0%)		5 (0.2%)	

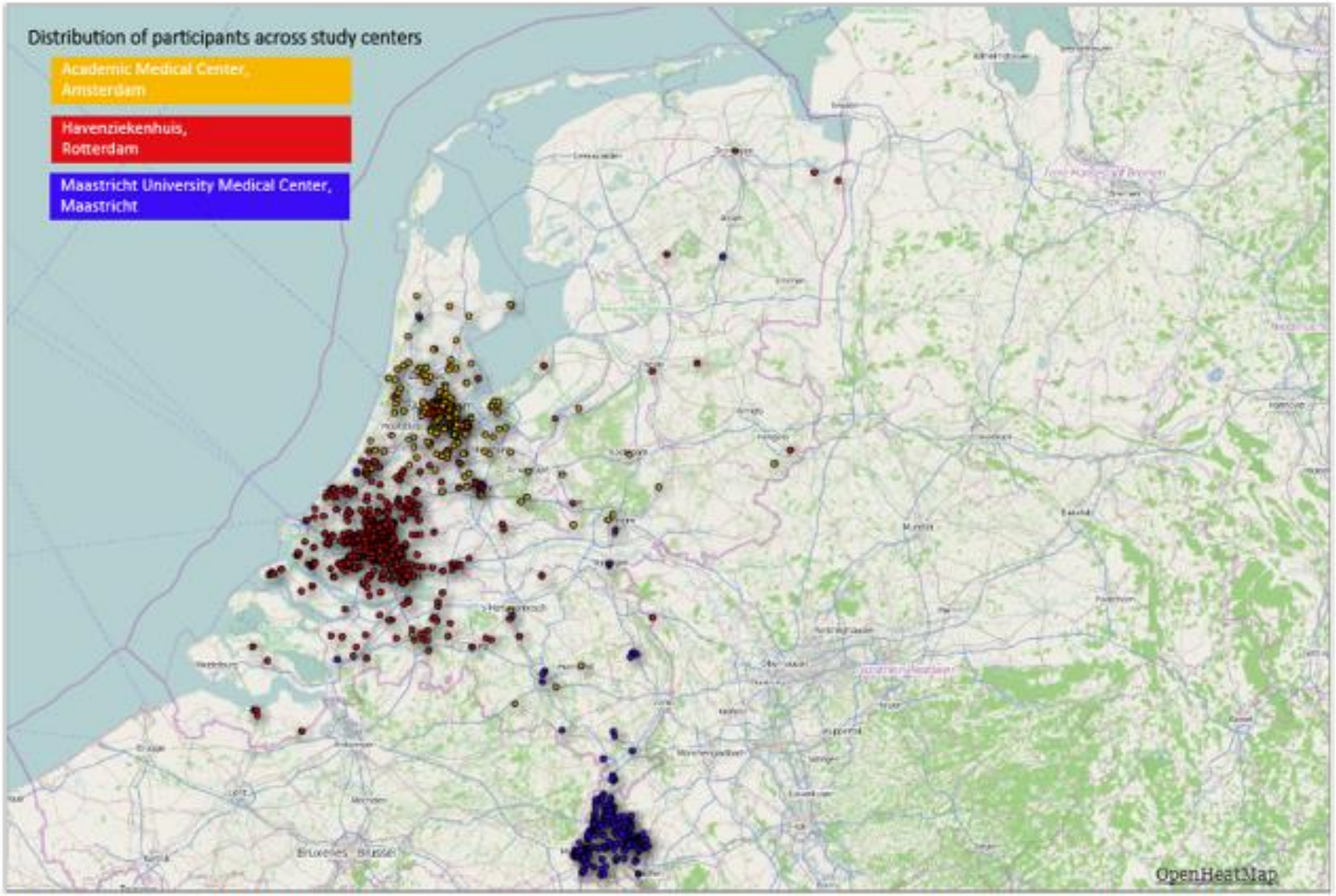


Figure 2 Geographic distribution of residences of participating travellers (n = 2001) throughout the Netherlands according to study center. i. Yellow circles represent participants from Tropencentrum AMC, Amsterdam. ii. Red circles represent participants from Travel Clinic Havenziekenhuis, Rotterdam. iii. Blue circles represent participants from Maastricht University Medical Center, Maastricht.

GENERAL CHARACTERISTICS

	Travellers (n=2001)*	Non-travelling household members (n=215)†
Sex		
Male	920 (46·0%)	80 (37·2%)
Female	1081 (54·0%)	135 (62·8%)
Age (years)	50·5 (32·8–60·7)	46·9 (25·7–55·8)
Education level		
No education, elementary school, or prevocational secondary education	243 (12·4%)	78 (36·4%)
Vocational secondary education	280 (14·2%)	37 (17·3%)
Senior general secondary education or education up to university	200 (10·2%)	45 (21·0%)
Higher professional education	642 (32·7%)	53 (24·7%)
Academic (university) education	595 (30·3%)	38 (17·8%)
Antibiotic use in previous 3 months		
No	1760 (90·1%)	189 (88·3%)
Yes	194 (9·9%)	25 (11·7%)
Travel in past year		
None	185 (9·5%)	27 (12·6%)
In Europe	915 (46·9%)	124 (57·7%)
Outside Europe	852 (43·6%)	64 (29·8%)
Chronic disease‡		
No	1500 (77·2%)	173 (82·0%)
Yes	443 (22·8%)	38 (18·0%)
Chronic bowel disease‡		
No	1912 (97·4%)	212 (99·1%)
Yes	51 (2·6%)	2 (0·9%)
Continent visited during travel§		
Asia	1016 (50·8%)	NA
Africa	633 (31·6%)	NA
America	326 (16·3%)	NA
Europe	21 (1·0%)	NA
Oceania	5 (0·2%)	NA
Duration of index travel (days)	20 (15·0–25·0)	NA
Purpose of index travel		
Holiday	1655 (84·2%)	NA
Work or internship	161 (8·2%)	NA
Visiting family or relatives	82 (4·2%)	NA
Other reason	66 (3·4%)	NA

Data are number (%) or median (IQR). NA=not applicable. *Some numbers do not add up to 2001 because of missing data. †Some numbers do not add up to 215 because of missing data. ‡Self-reported by traveller or household member. §If travellers visited multiple continents, only the main continent visited is presented in this table.

Table 1: **Baseline characteristics of travellers and non-travelling household members**

RESULTS ACQUISITION ESBL-E

	Number of travellers (n=1847)*	Number of travellers who acquired ESBL-E (n=633)†	ESBL-E incidence proportion (95% CI)‡	Number of travel-days	Mean (SD) duration of travel (days)	ESBL-E incidence per 100 person-days of travel (95% CI)§
Southern Asia	181 (9·8%)	136 (21·5%)	75·1 (68·4–80·9)	3727	20·6 (11·0)	7·2 (5·9–8·6)
Central and eastern Asia	84 (4·5%)	41 (6·5%)	48·8 (38·4–59·3)	1712	20·4 (10·8)	3·5 (2·5–4·7)
Western Asia	28 (1·5%)	12 (1·9%)	42·9 (26·5–60·9)	305	10·9 (7·5)	5·8 (3·0–9·9)
Northern Africa	81 (4·4%)	34 (5·4%)	42·0 (31·8–52·9)	981	12·1 (5·7)	4·5 (3·1–6·2)
Southeastern Asia	540 (29·2%)	200 (31.6%)	37·0 (33·1–41·2)	12 493	23·1 (11·6)	2·1 (1·8–2·4)
Caribbean and Central America	86 (4·7%)	24 (3·8%)	27·9 (19·5–38·2)	1653	19·2 (12·4)	1·7 (1·1–2·5)
Middle and eastern Africa	205 (11·1%)	57 (9·0%)	27·8 (22·1–34·3)	4060	19·8 (14·3)	1·6 (1·2–2·1)
Western Africa	106 (5·7%)	20 (3·2%)	18·9 (12·6–27·4)	1638	15·5 (11·1)	1·4 (0·8–2·0)
South America	180 (9·7%)	33 (5·2%)	18·3 (13·4–24·6)	4778	26·5 (14·7)	0·8 (0·5–1·1)
Southern Africa	116 (6.3%)	7 (1·1%)	6·0 (2·5–12·0)	2522	21·7 (8·6)	0·3 (0·1–0·6)
Northern America, Europe, and Oceania	17 (1·0%)	1 (<1·0%)	5·9 (1·1–27·0)	292	17·2 (11·3)	0·4 (0–1·6)

ESBL-E=extended-spectrum β-lactamase-producing Enterobacteriaceae. *Numbers do not add up to 1847 because 221 travellers visited more than one subregion (66 with ESBL-E acquisition) and destination information was missing for two. †Numbers do not add up to 633 because 66 travellers visited multiple subregions and destination information was missing for two. ‡Based on binomial distribution (Wilson's score interval). §Calculated with the maximum likelihood estimation method based on a constant acquisition rate with right-censored and interval-censored data.

***Table 2*: Incidence proportion and incidence per 100 person-days of travel for ESBL-E acquisition in Dutch travellers, by subregion**

GEOGRAPHICAL MAP OF ESBL-E ACQUISTION

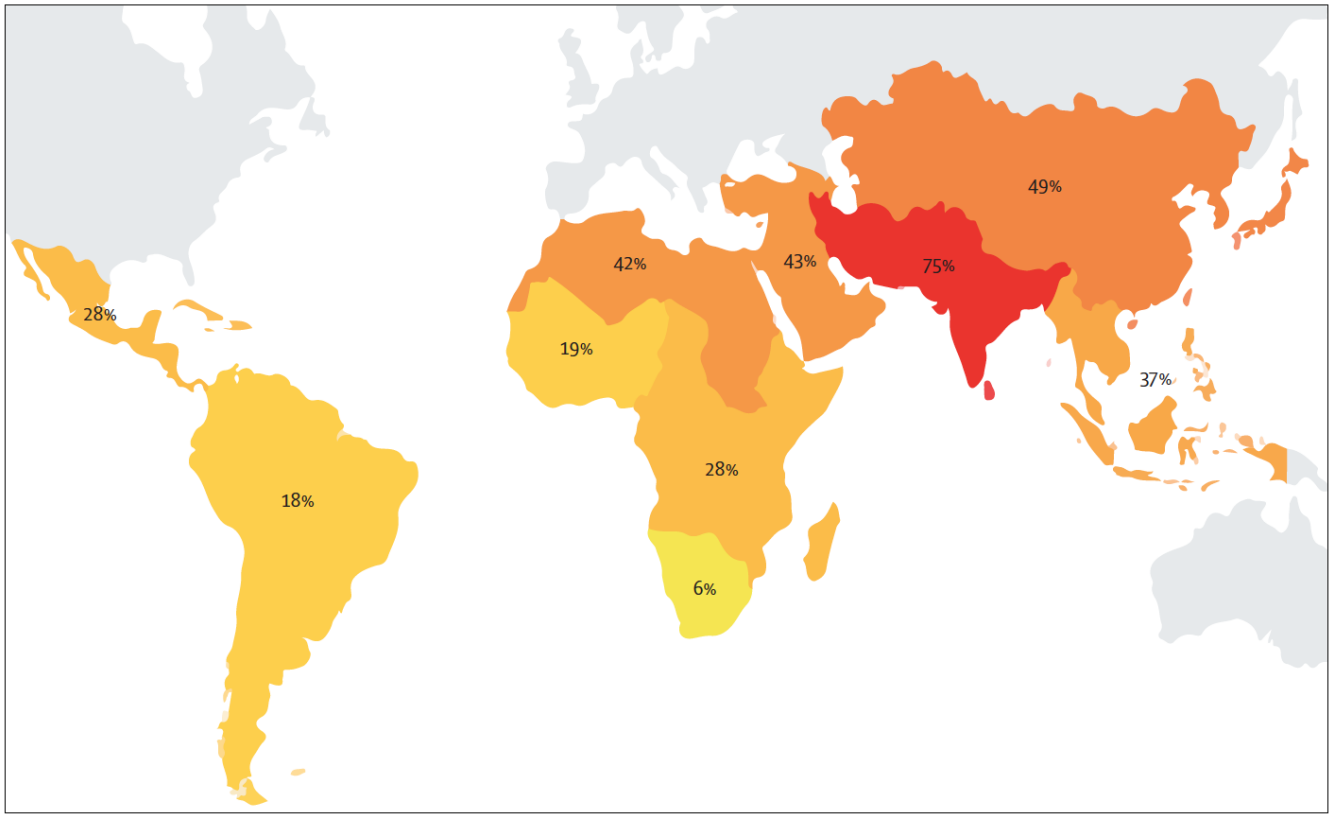


Figure 1: Percentages of travellers that acquired β-lactamase-producing Enterobacteriaceae per subregion, according to the United Nations geoscheme

Pre-travel ESBL-E carriage 122/2001 (6.1%)
ESBL-E acquisition 633/1847 (34.3%)

	Number of travellers at risk (n=1847)*	Number of travellers who acquired ESBL-E (n=633)†	Odds ratio (95% CI)‡	p value	Adjusted odds ratio (95% CI)§	p value
Pre-existing bowel disease						
No	1793 (97·3%)	606 (33·8%)	1·00	..	1·00	..
Yes	50 (2·7%)	24 (48·0%)	2·34 (1·26–4·34)	0·007	2·10 (1·13–3·90)	0·019
Beach holiday						
No	1404 (76·1%)	504 (35·9%)	1·00	..	1·00	..
Yes	441 (23·9%)	127 (28·8%)	0·72 (0·55–0·93)	0·010	0·73 (0·56–0·95)	0·021
Traveller's diarrhoea¶						
No	1085 (60·1%)	329 (30·3%)	1·00	..	1·00	..
During travel	593 (32·8%)	235 (39·6%)	1·56 (1·24–1·96)	<0·001	1·42 (1·12–1·80)	0·003
Immediately after travel	41 (2·3%)	14 (34·1%)	1·19 (0·58–2·44)	0·640	1·3 (0·63–2·68)	0·477
During travel and immediately after travel	87 (4·8%)	44 (50·6%)	2·42 (1·50–3·91)	<0·001	2·31 (1·42–3·76)	0·001
Antibiotic use during travel||						
No	1697 (92·8%)	553(32·6%)	1·00	..	1·00	..
Yes	132 (7·2%)	73 (55·3%)	2·65 (1·80–3·91)	<0·001	2·69 (1·79–4·05)	<0·001
Attendance of large (religious) gathering						
No	1744 (94·6%)	595 (34·1%)	1·00	..	1·00	..
Yes	100 (5·4%)	36 (36·0%)	0·56 (0·34–0·92)	0·020	0·57 (0·34–0·94)	0·028
Daily hand hygiene before meals						
None	782 (42·4%)	265 (33·9%)	1·00	..	1·00	..
Clean with alcohol	161 (8·7%)	69 (42·9%)	1·03 (0·71–1·51)	0·870	0·97 (0·66–1·44)	0·885
Clean with soap	666 (36·1%)	200 (30·0%)	0·82 (0·64–1·04)	0·100	0·77 (0·60–0·99)	0·044
Clean with alcohol and soap	235 (12·7%)	97 (41·3%)	1·03 (0·74–1·44)	0·860	1·12 (0·79–1·59)	0·518
Meal at street food stalls during travel						
Never	1248 (67·7%)	386 (30·9%)	1·00	..	1·00	..
Occasionally	513 (27·8%)	205 (40·0%)	1·37 (1·08–1·73)	0·010	1·33 (1·04–1·71)	0·022
Daily	83 (4·5%)	40 (48·2%)	2·09 (1·30–3·38)	0·003	1·78 (1·07–2·95)	0·025

PERSISTENT DIARRHEA

ESBL-E=extended-spectrum β-lactamase-producing Enterobacteriaceae. *Numbers do not add up to 1847 because of missing values. Valid percentages are reported after removal of missing values, which were assumed to be random. †Numbers do not add up to 633 because of missing values. The denominators for percentages are the numbers of travellers at risk given in the previous column. ‡Only adjusted for travel destination subregion, defined according to the United Nations geoscheme: Caribbean and Central America, middle and eastern Africa, central and eastern Asia, North America, Europe, and Oceania, southern Asia, southeastern Asia, western Asia, northern Africa, southern Africa, western Africa, and South America. §Adjusted for travel destination and travel variables shown in table. ¶Defined as ≥3 unformed stools within 24 h, with or without accompanying symptoms. ||Most frequently used to treat gastroenteritis (41 [31·1%] of 132 travellers), of whom 17 (41·5%) took them without consulting a doctor.

Table 3: Predictors for ESBL-E acquisition among travellers in the final adjusted logistic regression model

DURATION OF CARRIAGE OF ESBL-E

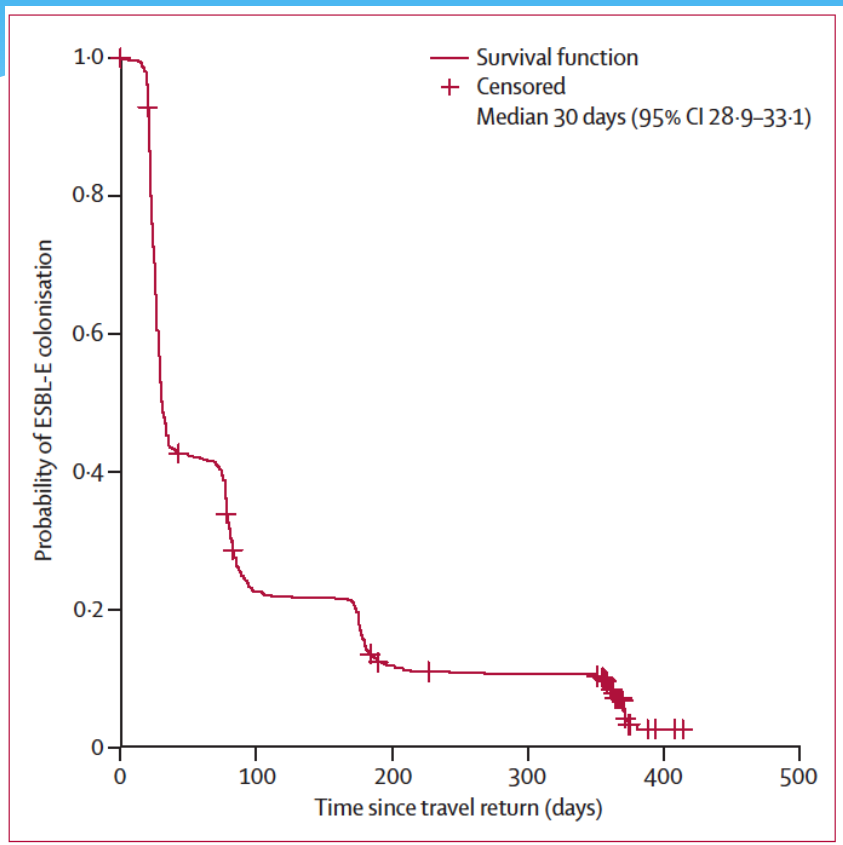
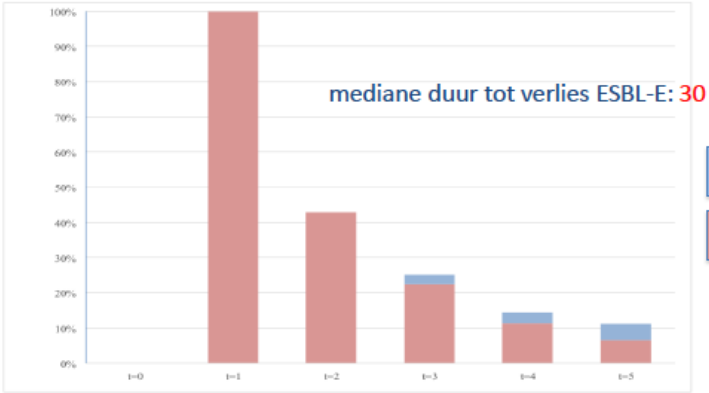


Figure 2: **Kaplan-Meier estimate of time to decolonisation of ESBL-E in travellers**
ESBL-E=extended-spectrum β-lactamase-producing Enterobacteriaceae.



CTX-M ENZYME GROUP 9 ESBLS median of 75 days

Transmission ESBL-E to householdmembers

zonder mathematisch model

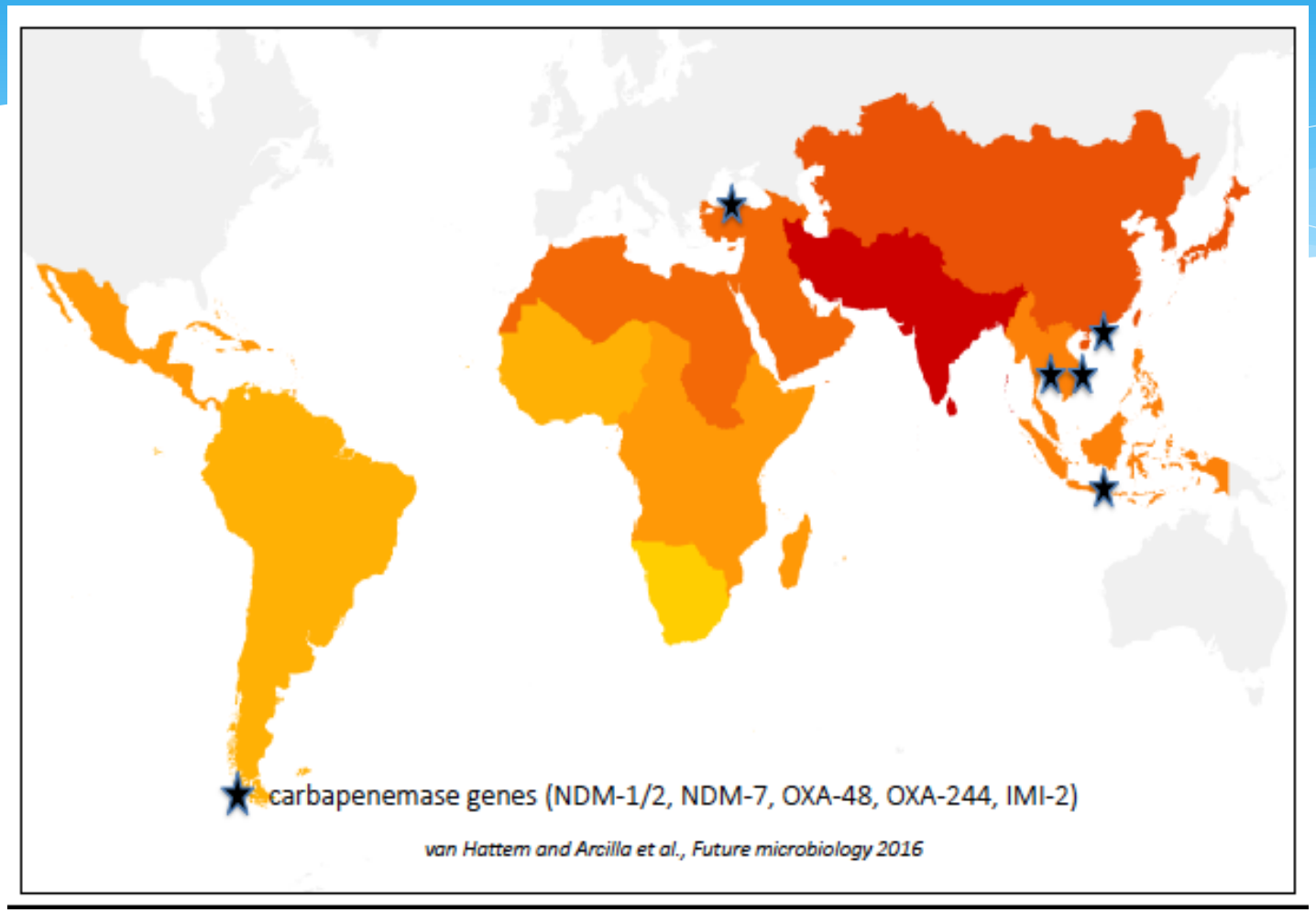
Onward transmission	Medereizigers	Niet-reizende huisgenoten	**Totaal**
transmissies / N "at risk"	10/105 (10%)	3/63 (5%)	**13/168 (8%)**

met mathematisch model

α - achtergrondtransmissie snelheid (per dag)	0.00073
β - directe transmissie snelheid (per gekoloniseerd persoon/dag)	0.0013
γ – dekolonisatie snelheid (per dag)	0.010

Transmissiekans van ESBL-E= 12%

Acquisition of CPE



5 travelers to Asia acquired CPE – none of them sought medical care – all but one had TD – one used AB – persistence of colonization up to 6 months in one – clonal transmission of OXA-244 to her spouse

Colistin resistance (mcr-1)

	Traveller with isolate 1	Traveller with isolate 2	Traveller with isolate 3	Traveller with isolate 4	Traveller with isolate 5	Traveller with isolate 6
Travel destination	Thailand, Vietnam, Cambodia, Laos	Tunisia	Peru, Bolivia, Colombia	China	China	Peru, Bolivia
Travel duration (days)	21	8	40	14	23	22
Age (years)	56	55	25	54	62	26
Sex	Female	Female	Female	Male	Female	Male
ESBL gene (ESBL group)	CTX-M-14 (CTX-M group 9)	CTX-M-1 (CTX-M group 1)	CTX-M-15 (CTX-M group 1)	CTX-M-65 (CTX-M group 9)	CTX-M-55 (CTX-M group 1)	CTX-M-55 (CTX-M group 1)
Minimum inhibitory concentration of antimicrobial drug (mg/L)*						
Amoxicillin-clavulanic acid	16	8	>16	16	8	4
Piperacillin-tazobactam	8	≤4	8	≤4	≤4	≤4
Cefotaxime	16	8	32	16	>32	>32
Cefoxitin	16	≤4	8	≤4	≤4	≤4
Ceftazidime	≤1	≤1	16	≤1	4	4
Cefepime	2	2	2	≤1	2	2
Imipenem	≤0·25	≤0·25	≤0·25	≤0·25	≤0·25	≤0·25
Meropenem	≤0·25	≤0·25	≤0·25	≤0·25	≤0·25	≤0·25
Gentamicin	>8	≤1	>8	≤1	>8	≤1
Tobramycin	8	≤1	>8	8	8	≤1
Nitrofurantoin	256	≤16	128	32	64	≤16
Co-trimoxazole	>8	>8	>8	≤1	>8	>8
Norfloxacin	>8	8	>8	2	>8	>8
Ciprofloxacin	>2	>2	>2	1	>2	>2
Colistin	4	4	4	4	4	8

ESBL=extended-spectrum β-lactamase. *Determined using Vitek-2, except for colistin for which E-test results are provided.

Table: **Characteristics of travellers and acquired fecal *Escherichia coli* isolates carrying the *mcr-1* gene**

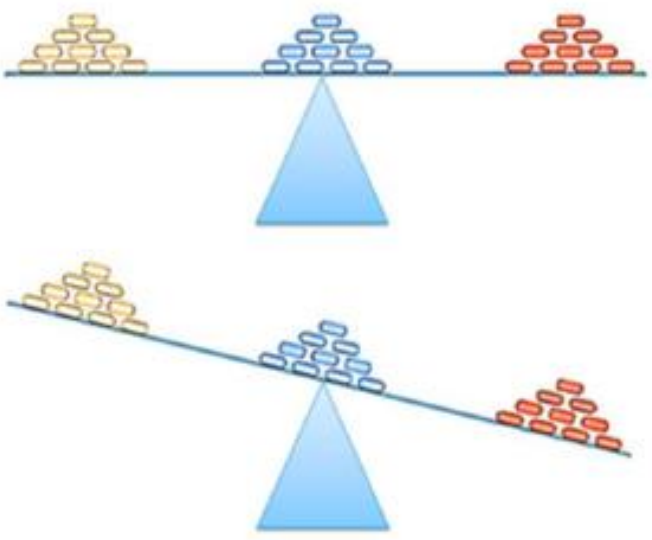
None medical care – None used AB – 5 had TD – Only short-term colonization (<1 month)

COMBAT STUDY - CONCLUSIONS

* Determine acquisition rate of multiresistant Enterobacteriaceae during foreign travel - **1/3 OF TRAVELERS (UP TO ¾ OF TRAVELERS TO INDIA)**
* Ascertain the duration of carriage of these micro-organisms - **MEDIAN DURATION OF CARRIAGE 30 DAYS**
* Determine the acquisition rate within households - **12%**
* Identify risk factors for acquisition, persistence of carriage and transmission of multiresistant Enterobacteriaceae - **ANTIBIOTIC USE, TRAVELER'S DIARRHEA, PRE-EXISTING BOWEL DISEASE**

The important rol of the microbioma

* Antibiotics, diarrhea and chronic bowel disorders → dysbiosis of bowel microbiota
* Dysbiosis → decreased colonization resistance in bowels → susceptibility for acquisition ESBL-E



Sullivan et al, Lancet Infect Dis 2001

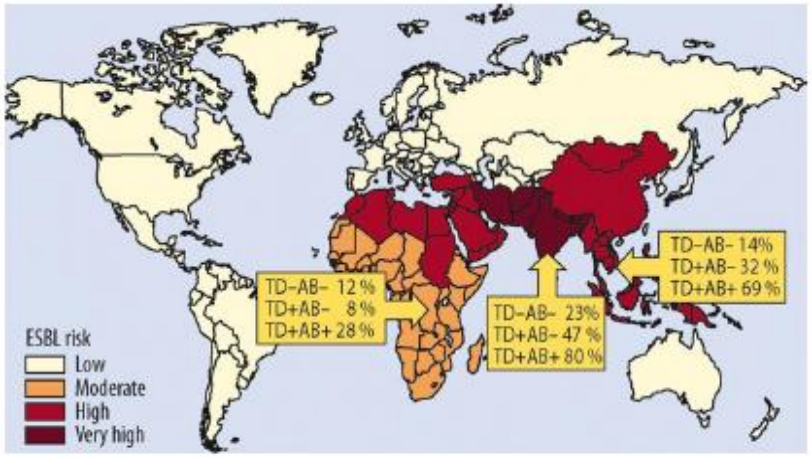
Youmans et al, Gut Microbes 2015

Sheehan et al, J Gastroenterol 2015

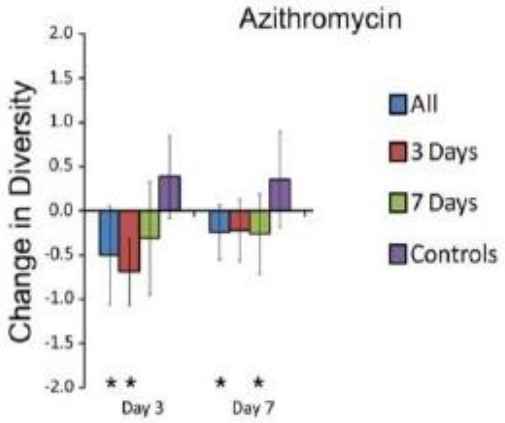
Round en Mazmanian, Nat Rev Immunol 2009

Consequences for pre-travel advice?

* Restrict use of antibiotics for self-limiting gastro-enteritis



Kantele et al. Clinical Infectious Diseases, 2015



Abeles et al, Microbiome 2016

* Prevent traveler's diarrhea
* Avoid food from street vendors

COMBAT studie groep:

AMC - Amsterdam

Menno de Jong

Constance Schultsz

Bram Goorhuis

Martin Grobusch

Jarne van Hattem

Erasmus MC - Rotterdam

Damian Melles

Henri Verbrugh

Maris Arcilla

Havenziekenhuis - Rotterdam

Perry van Genderen

Nicky Molhoek

MUMC – Maastricht

John Penders

Astrid Oude Lashof

Ellen Stobberingh

UMC - Utrecht

Martin Bootsma

Manon Haverkate

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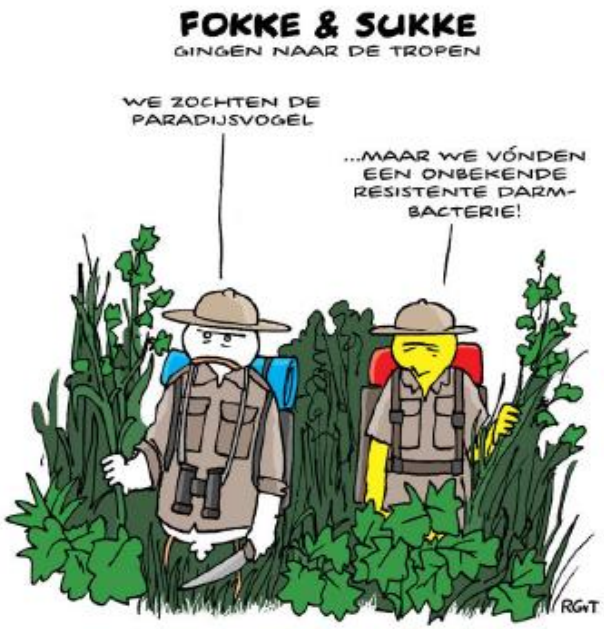
FOKKE & SUKKE
NEMEN EEN SOUVENIR MEE UIT DE TROPEN
VOOR DE KINDEREN: LEUK TRADITIONEEL HOUTSNIJWERK...
EN VOOR DE WETENSCHAP: EEN MULTIRESISTENTE DARMBACTERIE!
RGvT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WE ZOCHTEN DE PARADIJSVOGEL
...MAAR WE VÓNDEN EEN ONBEKENDE RESISTENTE DARM-BACTERIE!
RGvT