ESBL och ESBL-carba – ofarlig kolonisering eller ett folkhälsoproblem?

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Strama
Västar Götalandsregionen

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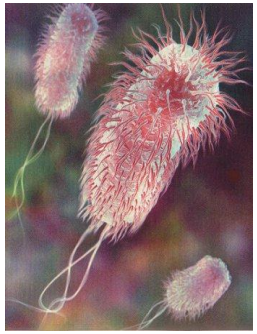
E.coli, Klebsiella (tarmbakterier)



- urinvägsinfektioner, blodförgiftning
- infekterade sår
- **ESBL-bildande** viss andel (ca 3%)
- lika vanligt i öppen vård som sluten vård

•7200 nya fall 2012 i Sverige

•2-4 fall ESBLCARBA per mån, 21 fall 2012

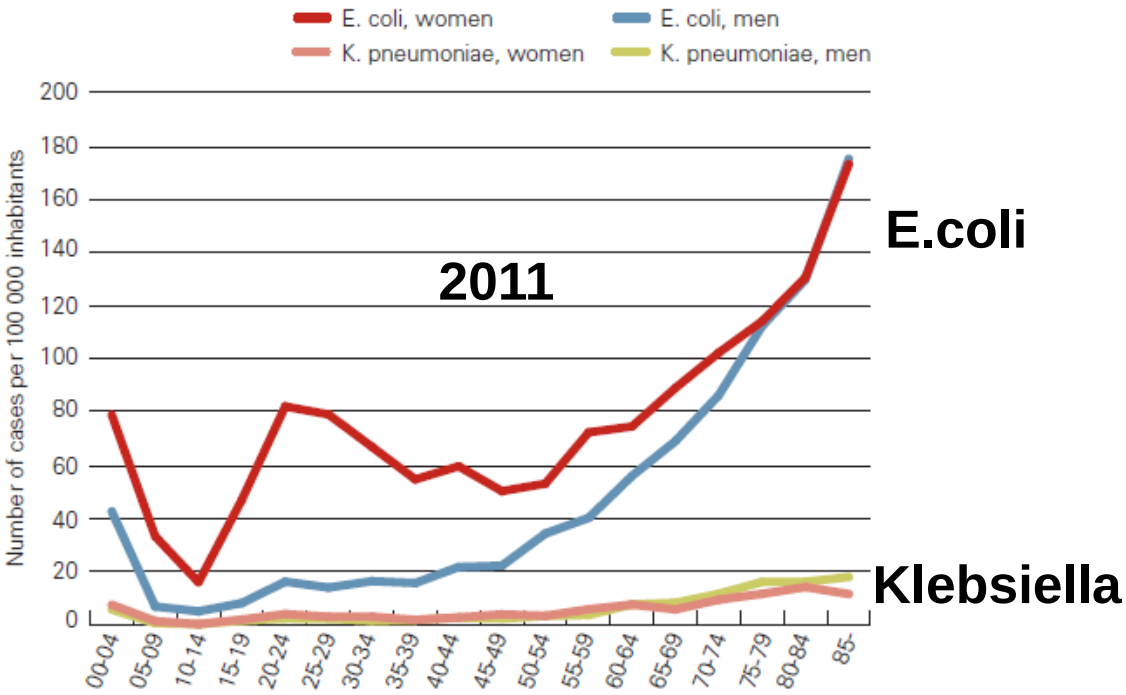


FIGURE 4.12. Age and gender distribution of *E.coli* and *K. pneumoniae* ESBL cases 2011.

www.smittskyddsinstitutet.se

ESBL$_{CARBA}$

- Senaste sortens ESBL
- Resistens mot
  - Penicilliner
  - Cefalosporiner
  - **Karbapenemer** (t ex Meropenem/imipenem)
- Samvarierar med annan resistens → det finns inget kvar att behandla med
- Anmälnings- och smittspårningspliktig enligt Smittskyddslagen sedan mars 2012

ESBL (Extended spectrum beta-lacatamase): enzymer, plasmidmedierade

ESBL-kategori	Ambler klass	Bryter ned	Karaktäriseras genom	Exempel på beta-laktamaser som ingår
$ESBL_A$	A	Cefalosporiner	Hämning med klavulansyra	**CTX-M (15,14)**, TEM-ESBL, SHV-ESBL
$ESBL_M$ (plasmid AmpC)	C	Cefalosporiner	Hämning med kloxacillin	CMY, DHA mfl
$ESBL_{CARBA}$	A	Cefalosporiner/ karbapenemer	Hämning med borsyra	**KPC** 2-13, GES 1-20
	B	Cefalosporiner/ karbapenemer	Hämning med dipikolinsyra	**Metallobetalaktamaser** (**VIM** 1-33, **NDM** 1-6, IMP 1-33 m fl)
	D	Karbapenemer	Ingen tillgänglig hämmare **Genotypisk detektion**	**OXA-48** m fl OXA-liknande karbapenemaser

Karbapenemresistens

- Metallo beta lactamas (MBL)
  - pseudomonas, acinetobacter, stenotrophomonas (VIM, IMP; NDM-1)
  - Enterobacteriaceae (NDM-1, VIM)

- K. pneumoniae karbapenemaser (KPC -2, 3)
  - K. pneumoniae och E. coli

- Oxacillinaser (OXA-48 m fl)

meropenem: lapp= I/R, **MIC>0,25 mg/L (S)**
(imipenem sämre än meropenem)

OBS!

- Poriner, (pumpar) + AmpC o/e ESBL
  - Enterobacter, E. coli, K. pneumoniae
  - Pågående karbapenembehandling

Reported cases of carbaNS Enterob.aceae

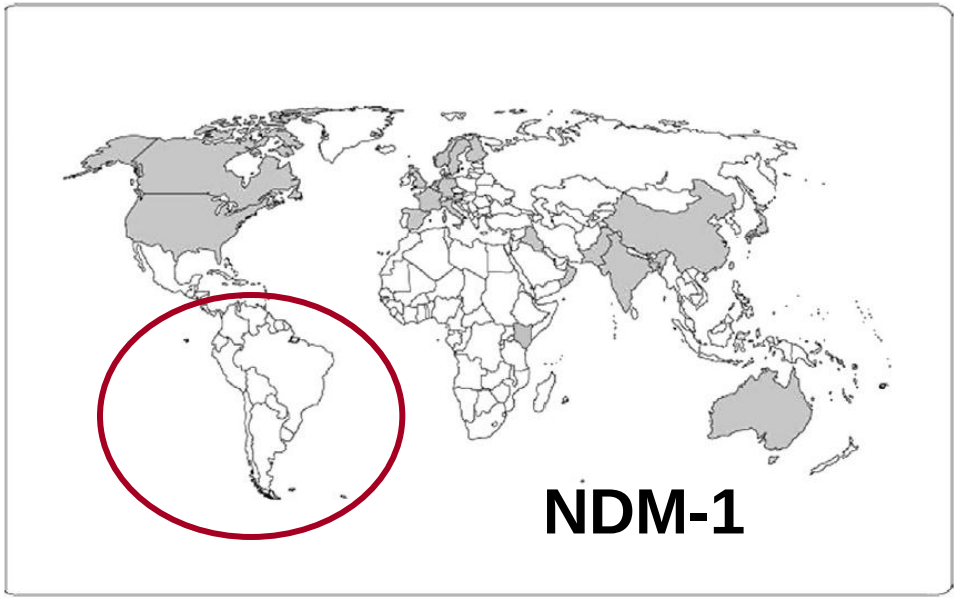
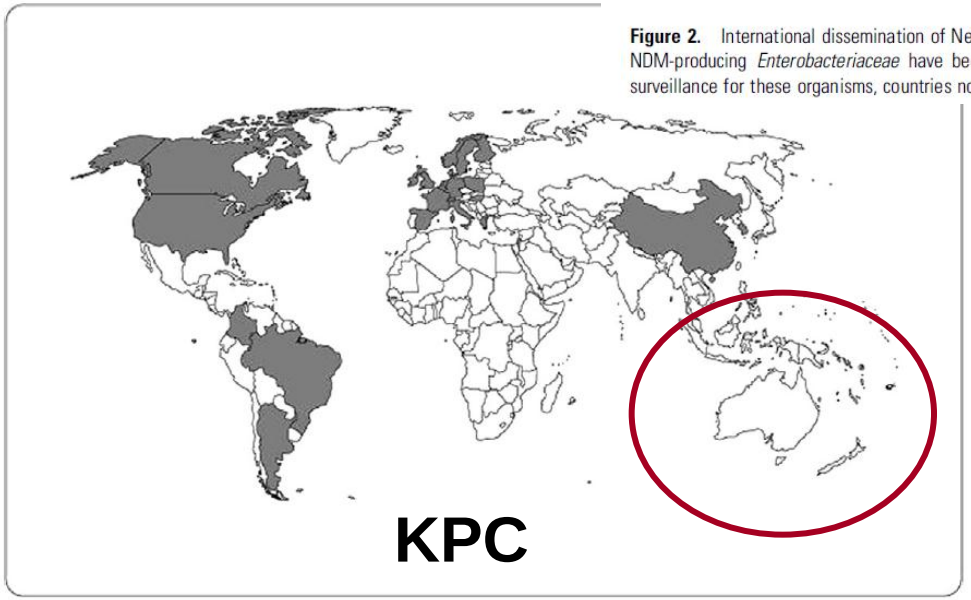


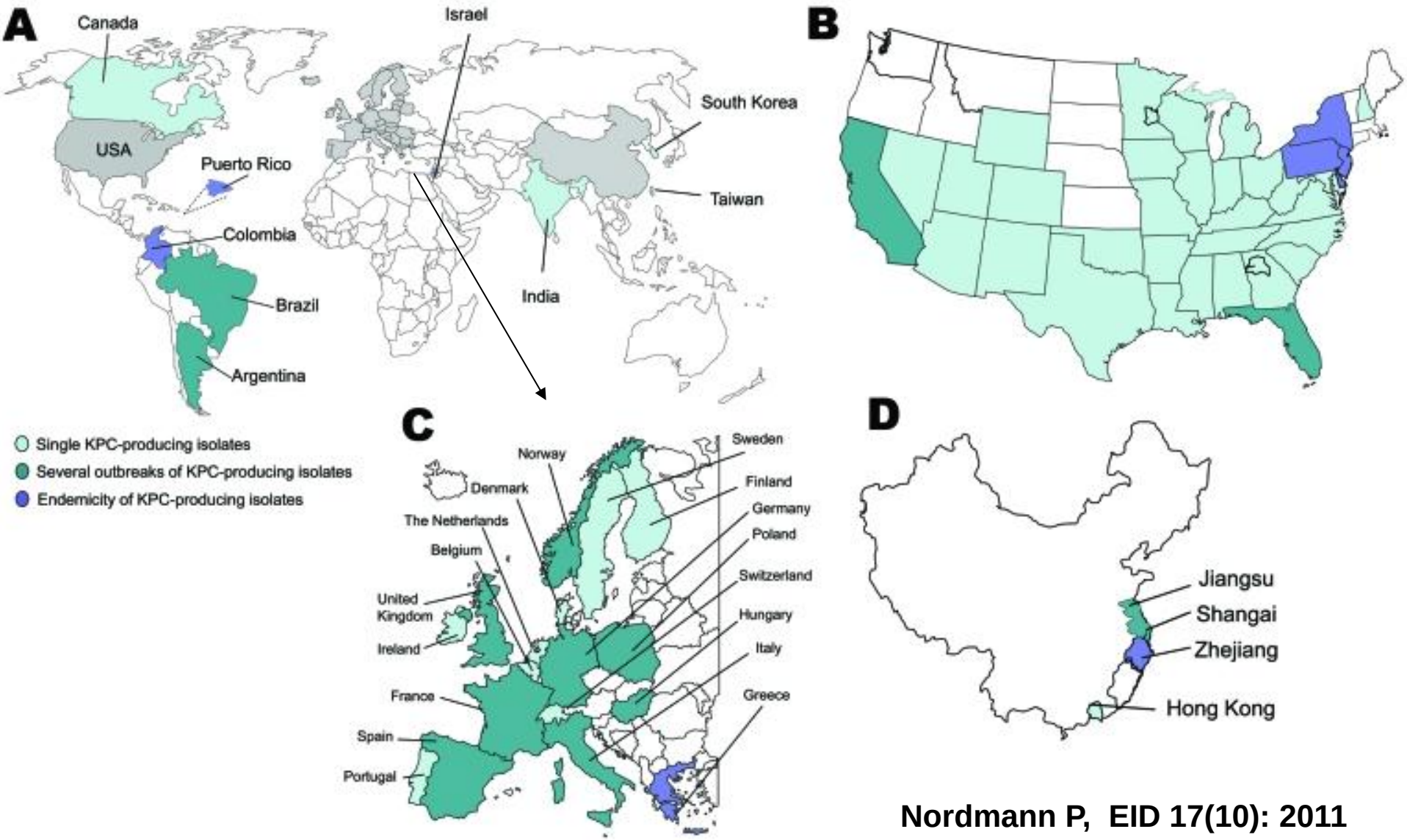
Figure 2. International dissemination of New Delhi metallo-β-lactamase (NDM)–producing *Enterobacteriaceae*. This map indicates countries where NDM-producing *Enterobacteriaceae* have been described in published reports available as of 11 February, 2011. Because of lack of systematic surveillance for these organisms, countries not highlighted in this figure might also have unreported NDM-producing *Enterobacteriaceae*.



Gupta N, CID 2011

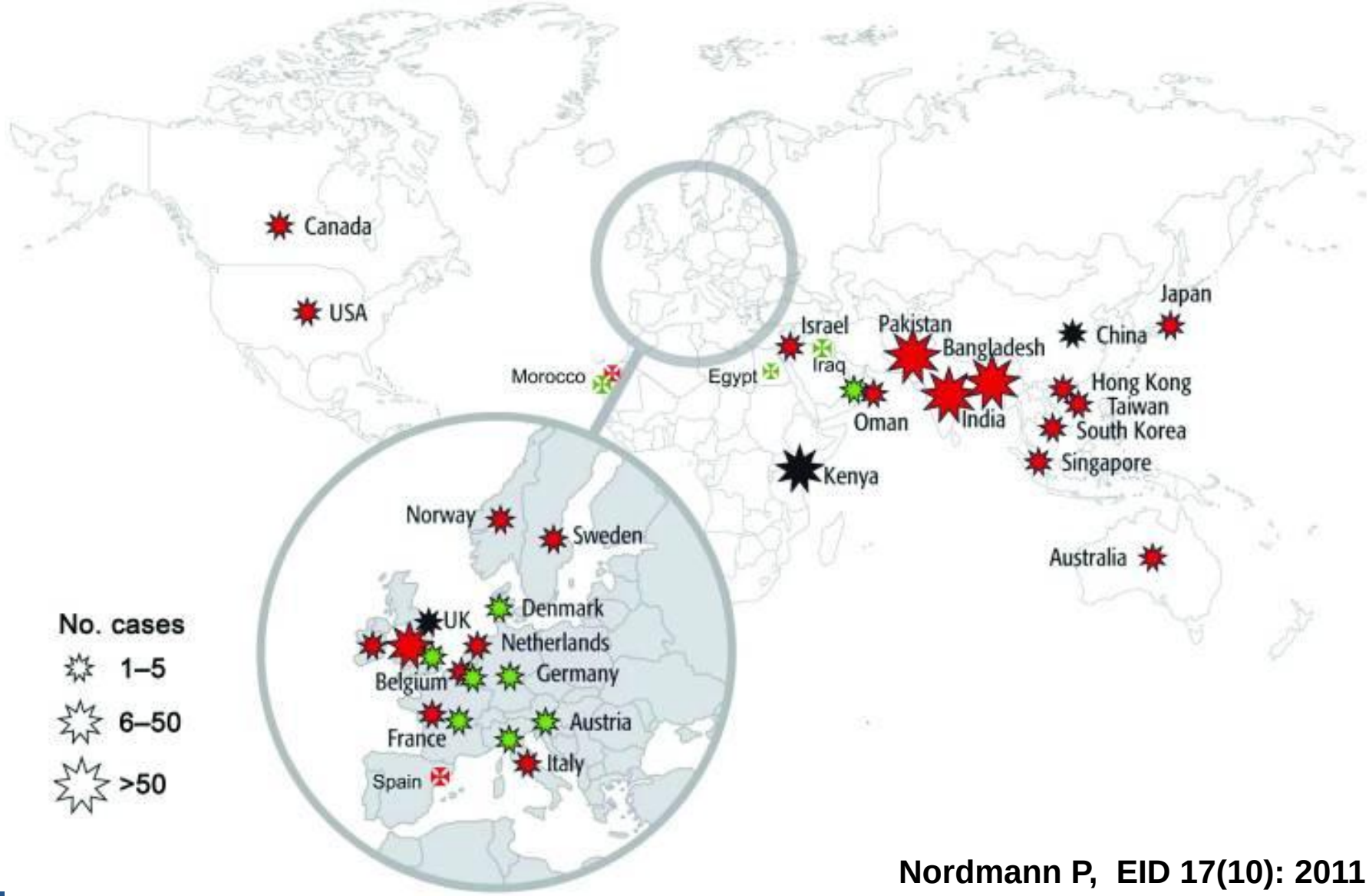
Figure 1. International dissemination of *Klebsiella pneumoniae* carbapenemase (KPC)–producing *Enterobacteriaceae*. This map indicates countries where KPC-producing *Enterobacteriaceae* have been described in published reports available as of 11 February, 2011. Because of lack of systematic surveillance for these organisms, countries not highlighted in this figure might also have unreported KPC-producing *Enterobacteriaceae*.

KPC - global förekomst



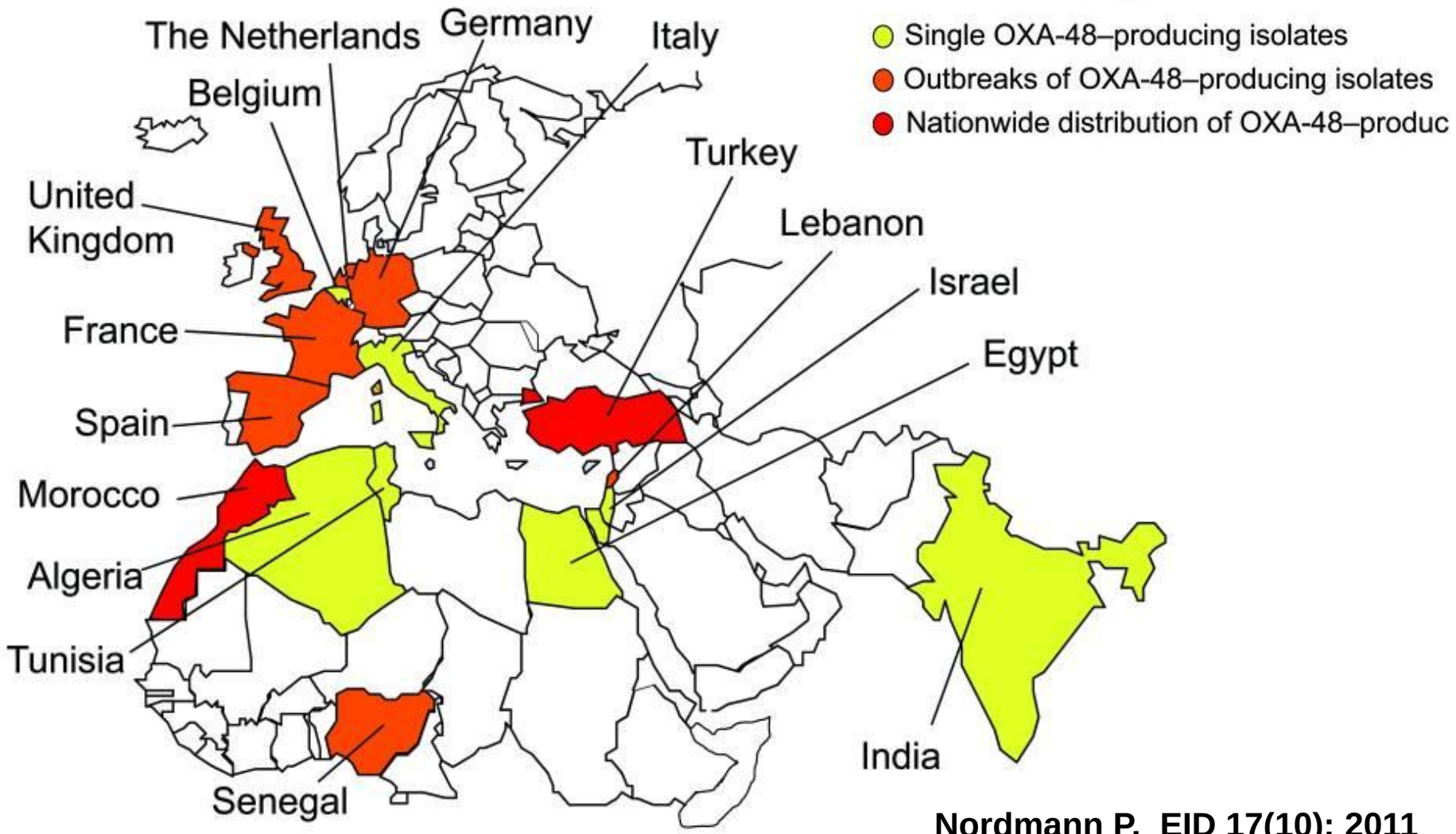
Nordmann P, EID 17(10): 2011

NDM-1 - global förekomst



Nordmann P, EID 17(10): 2011

OXA-48 - global förekomst



Nordmann P, EID 17(10): 2011

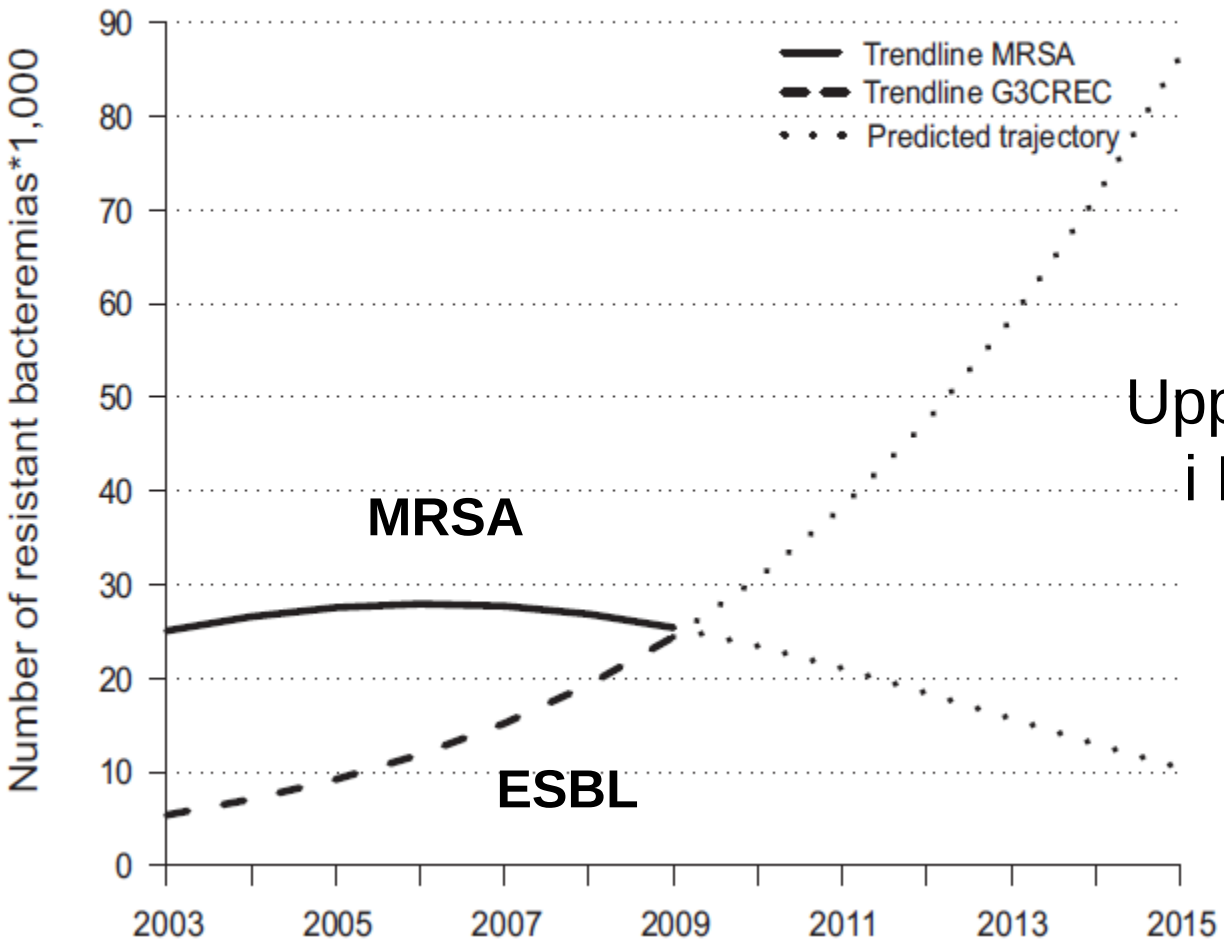
Carbapenemas-producing Enterobacteriaceae UK 2003-2011(03)

Numbers of isolates of Enterobacteriaceae from UK labs confirmed to have carbapenemases

	IMP	VIM	KPC	OXA-48	NDM	IMI	KPC+VIM
2003	1	1	1				
2004			3				
2005							
2006	3	1					
2007			1	1			
2008	1	2	5	9	5		
2009	9	4	13	15	32		
2010	9	26	229	29	44	2	
2011		19	31	5	7		1

www. hpa.org.uk

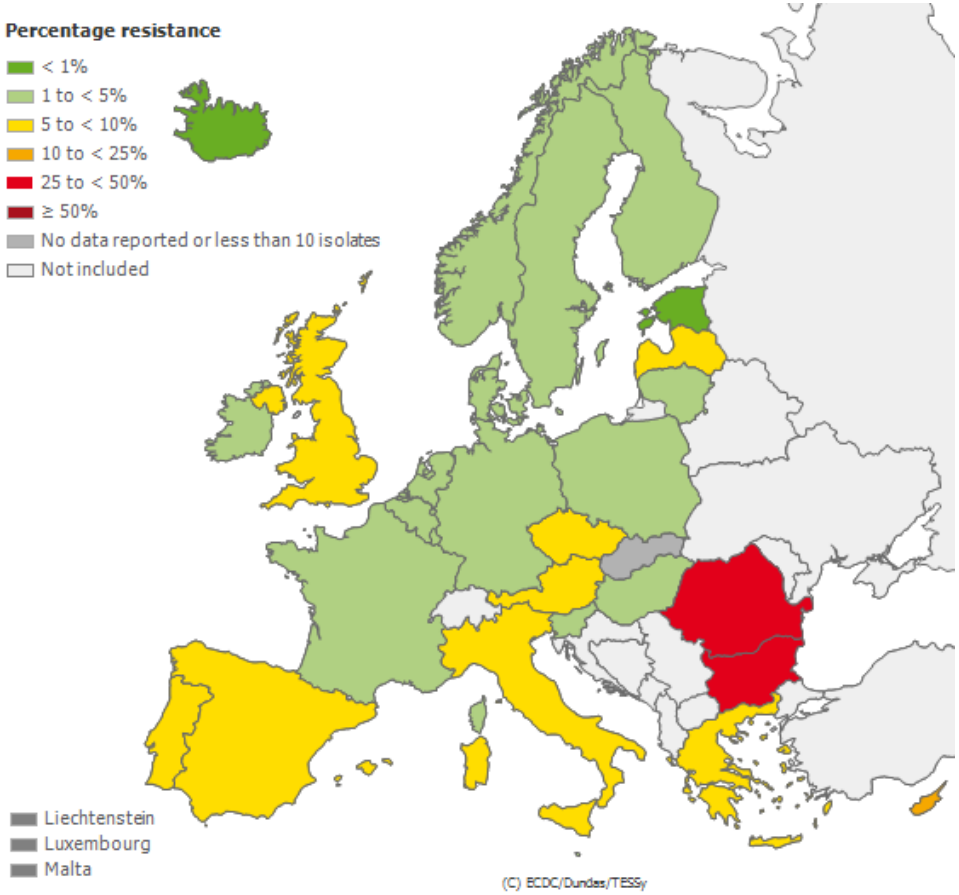
Finns det skäl till oro?



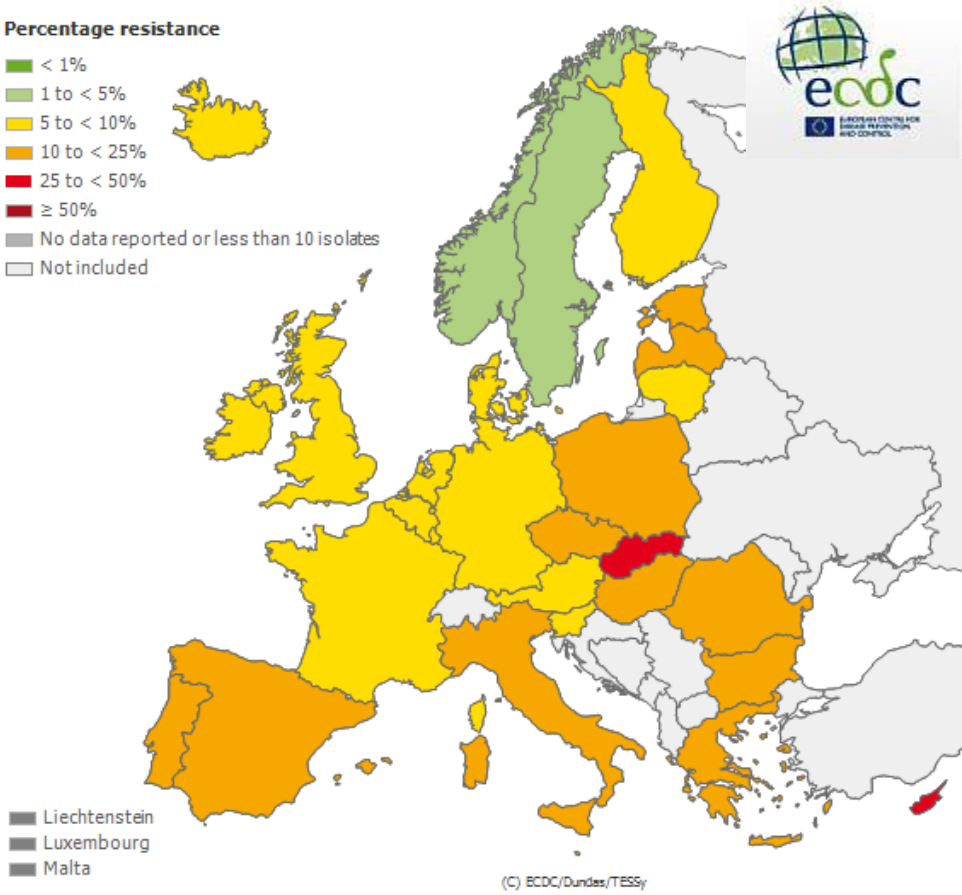
Uppskattad förekomst i Europa tom 2015 utifrån trend för 2003-2009

Marlieke E, PLOS medicine, 8 (10), 2011

Andel E. coli med ESBL, blodförgiftning, EARS-net 2006 → 2011



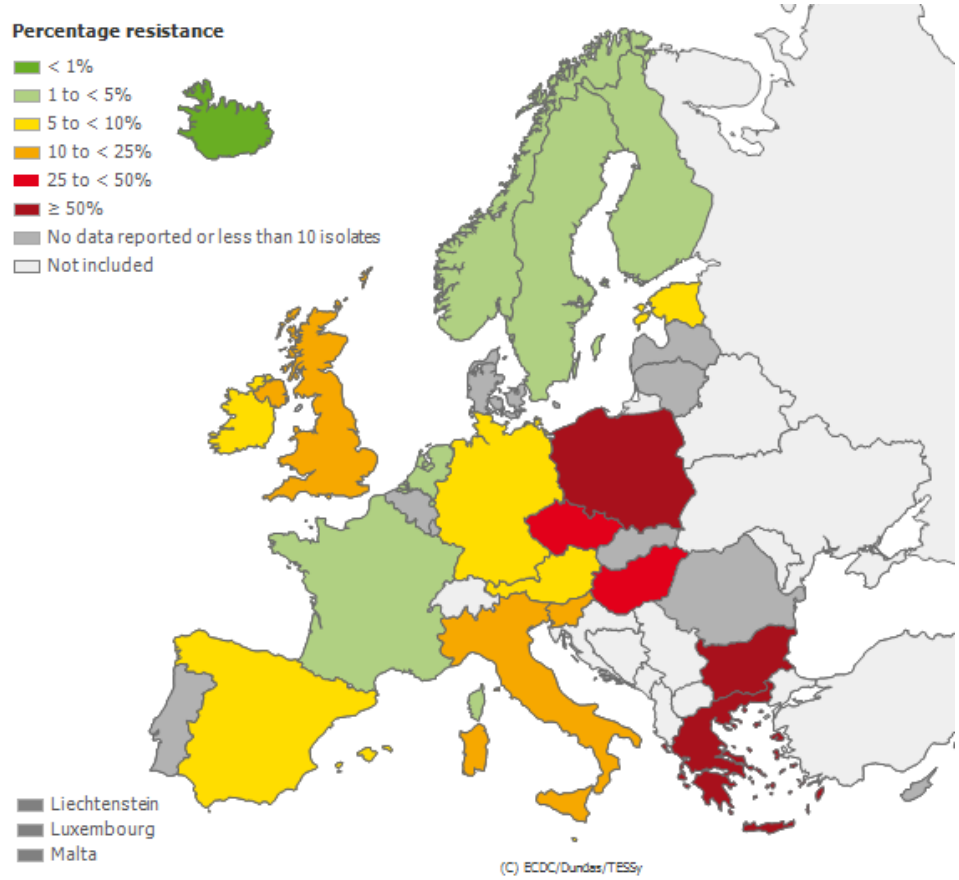
2006



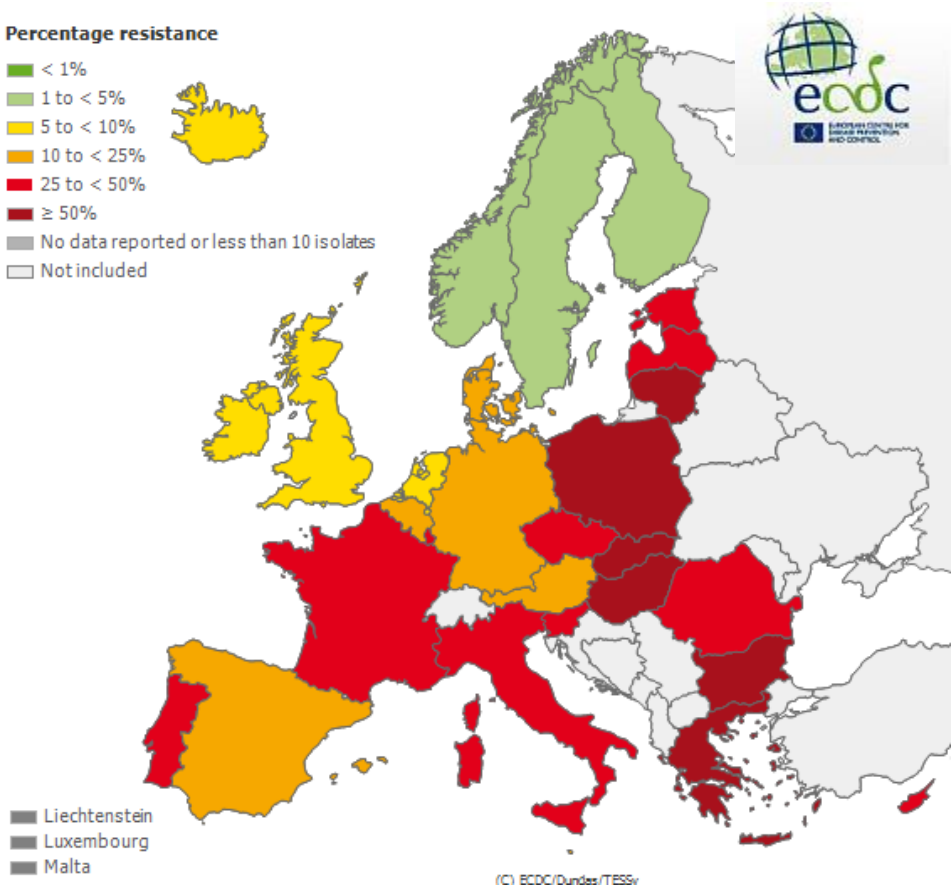
2011

www.ecdc.europa.eu/en/activities/surveillance/**EARS-Net**

Andel ESBL-bildande Klebsiella, blodförgiftning, EARS-net 2005 → 2011



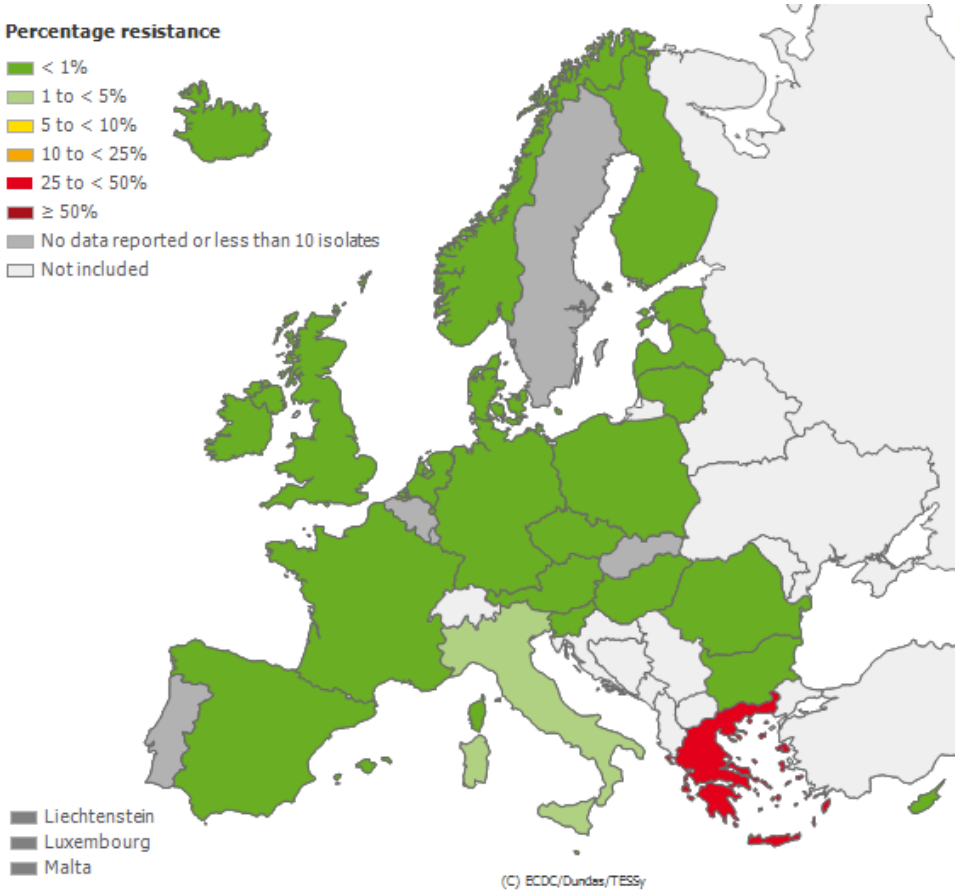
2005



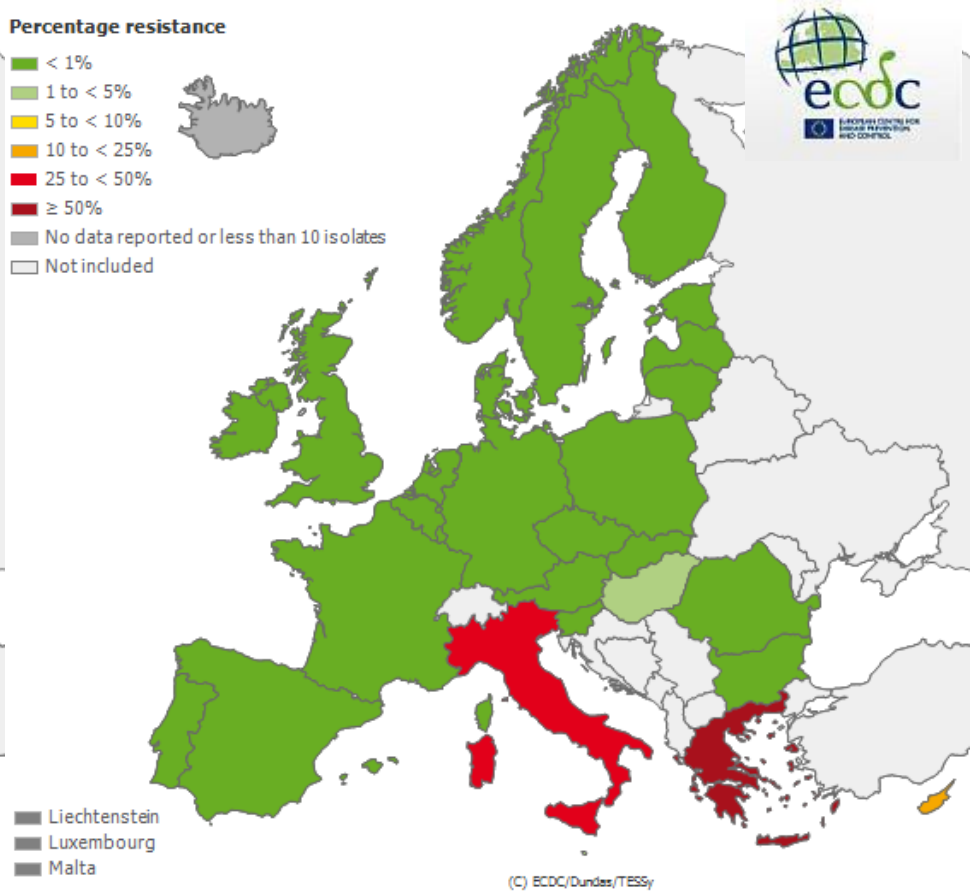
2011

www.ecdc.europa.eu/en/activities/surveillance/**EARS-Net**

Andel Klebsiella med ESBLCARBA, blodförgiftning, EARS-net 2006 → 2011



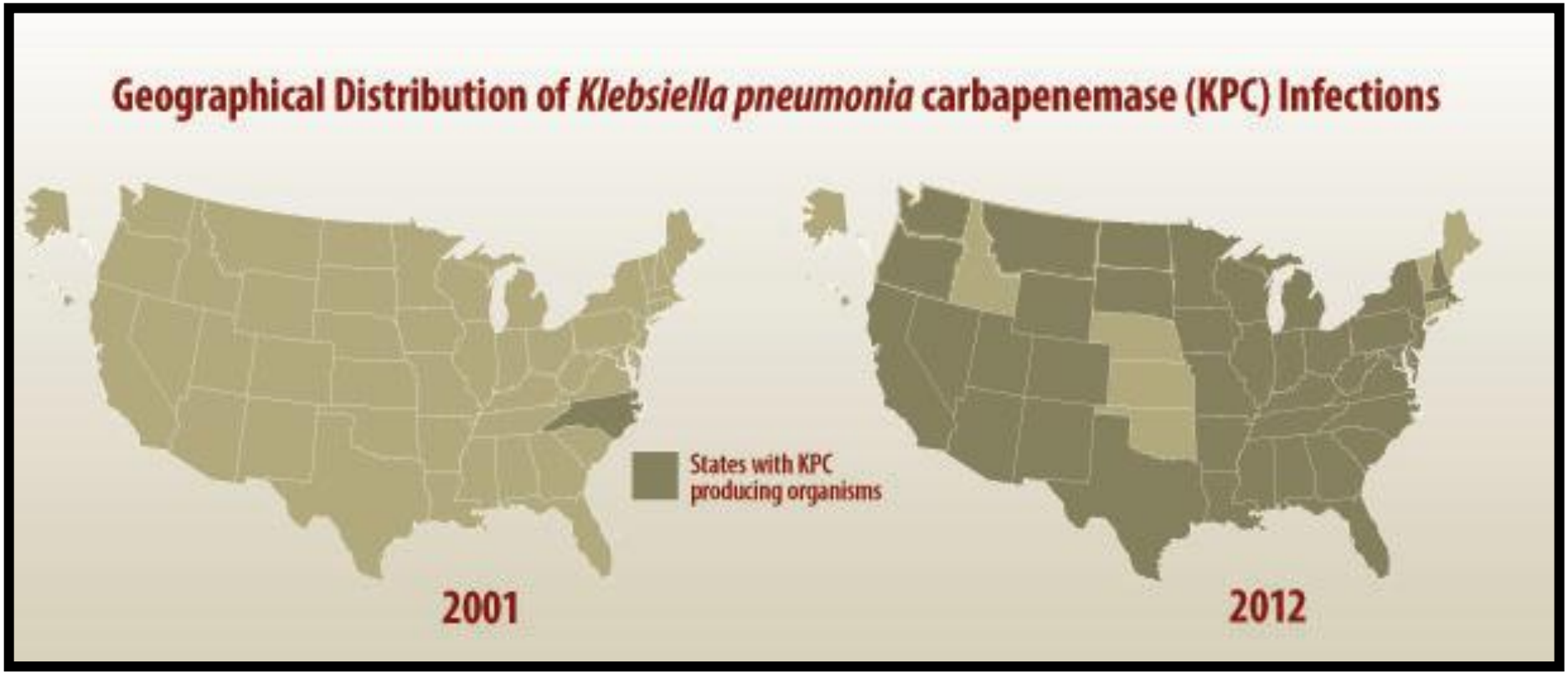
2006



2011

www.ecdc.europa.eu/en/activities/surveillance/**EARS-Net**

Klebsiella med ESBLCARBA i nästa alla USAs stater! ca 10 år



CRE i odlingar i USA

TABLE 2. Number of Enterobacteriaceae isolates, percentage reported to be tested against carbapenems, and percentage reported as carbapenem-resistant,* by data source, year, and type of organism — United States, National Nosocomial Infections Surveillance system (NNIS), National Healthcare Safety Network (NHSN), and the Surveillance Network–USA (TSN)†

VRI: 1,2 → 4,2 (10,4) %

	NNIS (2001)			NHSN (2011)		
Type of organism	No. of isolates	Reported as tested against ≥1 carbapenem No. (%)	Reported as carbapenem-resistant* No. (%)	No. of isolates	Reported as tested against ≥1 carbapenem No. (%)	Reported as carbapenem-resistant* No. (%)
Klebsiella pneumoniae and *oxytoca*	654	253 (38.7)	4 (1.6)	1,902	1,312 (69.0)	136 (10.4)
Escherichia coli	1,424	421 (29.6)	4 (1.0)	3,626	2,348 (64.8)	24 (1.0)
Enterobacter aerogenes and *cloacae*	553	288 (52.1)	4 (1.4)	1,045	728 (69.7)	26 (3.6)
Total	**2,631**	**962(36.6)**	**12 (1.2)**	**6,573**	**4,388 (66.8)**	**186 (4.2)**

Odlingar akut sjukhus 0→1,4 (5,3) %

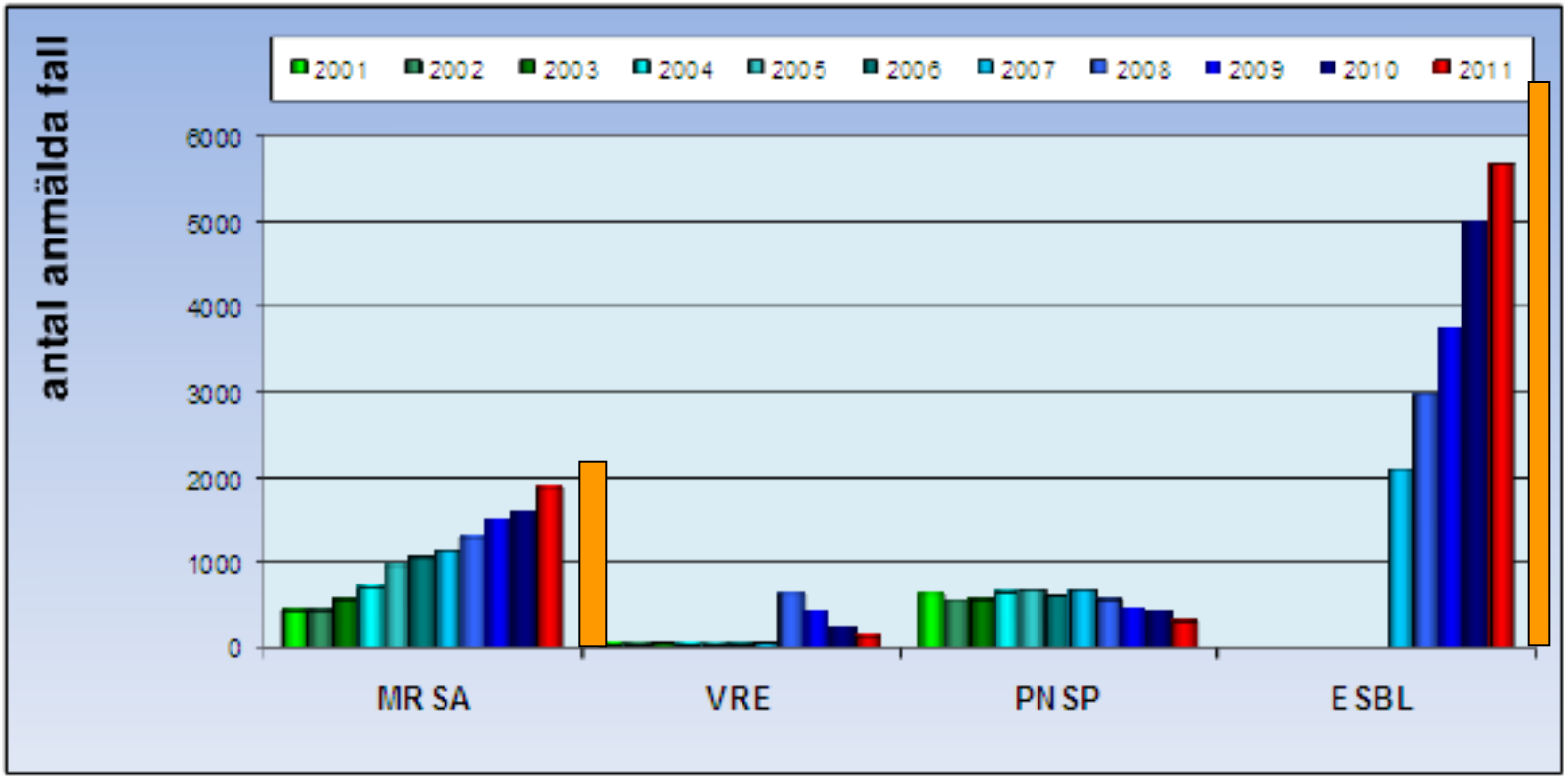
	TSN (2001)			TSN (2010)§		
Type of organism	No. of isolates	Reported as tested against ≥1 carbapenem No. (%)	Reported as carbapenem-resistant* No. (%)	No. of isolates	Reported as tested against ≥1 carbapenem No. (%)	Reported as carbapenem-resistant* No. (%)
Klebsiella pneumoniae	19,522	19,522 (100.0)	0 —	11,155	11,155 (100.0)	593 (5.3)
Esherichia coli	47,603	47,603 (100.0)	0 —	31,890	31,890 (100.0)	32 (0.1)
Enterobacter aerogenes and *cloacae*	14,764	14,764 (100.0)	3 (0)	5,768	5,768 (100.0)	69 (1.2)
Total	**81,889**	**81,889 (100.0)**	**3 (0)**	**48,813**	**48,813 (100.0)**	**694(1.4)**

* Intermediate or resistant to imipenem, meropenem, or doripenem.
† NNIS and NHSN include Enterobacteriaceae reported from hospital infections (i.e., intensive-care unit central-line–associated bloodstream infections, intensive-care unit catheter-associated urinary tract infections, and surgical site infections after colon surgery or coronary artery bypass grafting). TSN includes Enterobaceriaceae isolates from clinical cultures from acute-care hospitals submitted to participating laboratories.
§ Includes isolates reported during January–June 2010.

MMWR, mars 2013

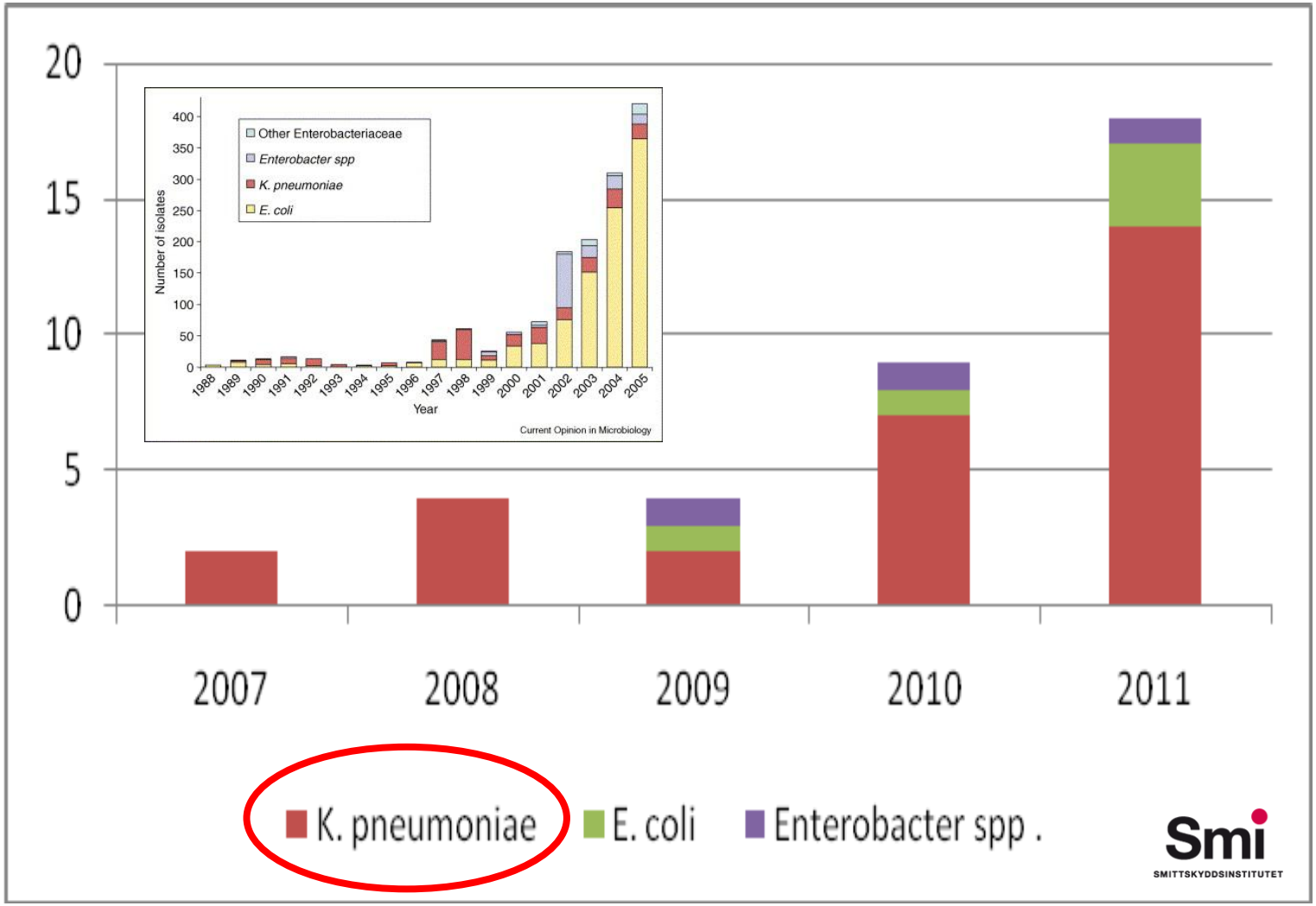
Anmälningspliktig resistens –

MRSA: meticillinresistenta S.aureus; VRE: vankomycinresistenta enterokocker;
PNSP: pneumokocker med nedsatt känslighet för penicillin; ESBL: E.coli och Klebsiella med ESBL



Smi
SMITTSKYDDSINSTITUTET

Antal fall av tarmbakterier med ESBLCARBA Sverige 2007-2012

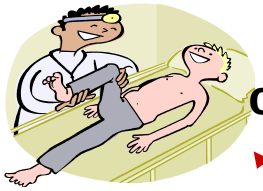


Majoriteten är importfall!

Varifrån kommer de resistenta tarmbakterierna?

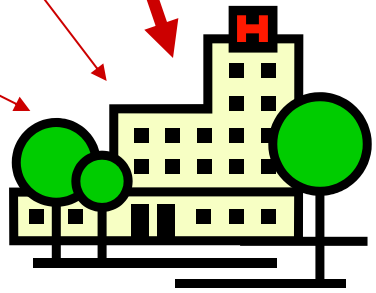
Samhället:
familjen
husdjur
boskap
livsmedel
vatten

Import:
patienter
resenärer
livsmedel



vård-central

sjukhem



Vården

Allt fler av oss blir bärare i tarmen!

30 % riskerar att bära på resistenta bakterier efter utlandsresa till Sydostasien, Egypten, Turkiet, Mellanöstern

Indien: 80 procent
Egypten: 50 procent
Thailand: 30 procent

Peru: 36 procent
Sydafrika: 27 procent
Tanzania: 24 procent

ESBL i livsmedel i Sverige

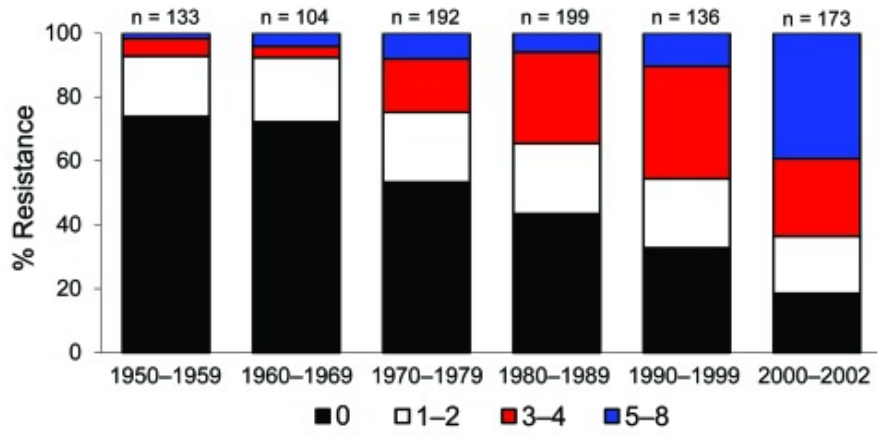
Levande djur: 54%
Kött: 15-95%

Levande djur: <1 %
Kött: 0-8%

Levande djur: 1.6%
Kött: 2-13 %

STATENS VETERINÄRMEDICINSKA ANSTALT

Tilltagande multiresistens hos E. coli både hos djur o människa, USA, 1950-2002

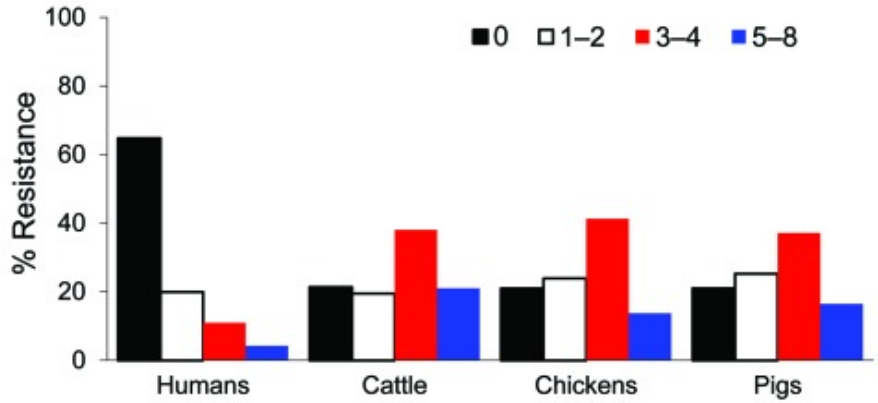


R ; 5-8 antibiotika

R; 1 antibiotika

Change in antimicrobial drug resistance patterns among *Escherichia coli* i

Figure 2



Homo nötdjur kyckling gris

R; minst 3 antibiotika
7→ 64 %

Tadessa EID 2012

Strama Västra Götaland
Samverkan mot antibiotikaresistens

Vi kan inte stoppa men kanske bromsa utvecklingen vi måste undvika smittspridning inom vården!

Goda hygienrutiner i samhället och i vården

Minska infektions-bördan

Behandla utifrån riktlinjer – bara när det behövs!

“Proven methods for preventing spread of MDRGNR”

- ”Proven” – inte mycket!
  - fr a utbrottsrapporter
  - S. Goddard, Am JIC 2011, review ESBL
    → 999 artiklar, 10 acceptabla, 0 riktigt bra!

- Vårdhygien terminologi→ inga uniforma definitioner!

  Dettenkofer M, J Hosp Infect 2011

  “isolation” (kohortvård):
  - ‘quarantine type’ separation with designated staff
  - single room
  - separated part of a room with “contact precautions”

Proven methods for preventing spread of MDRGNR

- MDR – inga uniforma definitioner!
  - vi blir avtrubbade
    - MRB ökar
    - nya än värre resistensmekanismer dyker upp
  - A-P Magiorakos, CMI 2011

- MDRGNR – arten spelar roll!
  - icke-fermenterande: acinetobacter, pseudomonas
  - *Enterobacteriacea:*
    - klebsiella, enterobacter, serratia,
    - E.coli

Vad ska vi reagera på?

Patienten
riskfaktorerna
typ av vård

Bakterien
arten
klonen

Resistensen
mekanismen
grad av resistens

När hettar det till?

agens	Risk faktorer hos patienten			
	Pos. i feces, enbart	Pos. flera lokaler	Risk faktorer	Diarré
ESBL bara				X
MDR + ESBL				
CarbaNS IF				
CarbaNS, XDR Enterob.aceae				

KPC - producerande K. pneumoniae, ST258 på neonatal avd
NDM-1 producerande E. coli, ST131 i samhället

ESBL: K. Pneumoniae > E. coli smittspridning

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]

[1]Institute for Infectious Diseases, University of Bern, and [2]Department of Infectious Diseases, University Hospital of Bern, Switzerland

Background. Studies about transmission rates of extended-spectrum β-lactamase (ESBL)–producing Enterobacteriaceae in hospitals and households are scarce.

Methods. Eighty-two index patients with new carriage of ESBL-producing *Escherichia coli* (ESBL-*Ec*; n = 72) or ESBL-producing *Klebsiella pneumoniae* (ESBL-*Kp*; n = 10) and their hospital (n = 112) and household (n = 96) contacts were studied prospectively from May 2008 through September 2010. Isolates were phenotypically and molecularly characterized (sequencing of *bla* genes, repetitive extragenic palindromic polymerase chain reaction, pulse-field gel electrophoresis, and multilocus sequence typing). Transmission was defined as carriage of a clonally-related ESBL producer with identical bla_{ESBL} gene(s) in the index patient and his or her contact(s).

Results. CTX-M-15 was the most prevalent ESBL in ESBL-*Ec* (58%) and ESBL-*Kp* (70%) in the index patients. Twenty (28%) ESBL-*Ec* isolates were of the hyperepidemic clone ST131. In the hospital, transmission rates were 4.5% (ESBL-*Ec*) and 8.3% (ESBL-*Kp*) and the incidences of transmissions were 5.6 (*Ec*) and 13.9 (*Kp*) per 1000 exposure days, respectively. Incidence of ESBL-*Kp* hospital transmission was significantly higher than that of ESBL-*Ec* ($P < .0001$), despite implementation of infection control measures in 75% of ESBL-*Kp* index patients but only 22% of ESBL-*Ec* index patients. Detection of ESBL producers not linked to an index patient was as frequent (ESBL-*Ec*, 5.7%; ESBL-*Kp*, 16.7%) as nosocomial transmission events. In households, transmission rates were 23% for ESBL-*Ec* and 25% for ESBL-*Kp*.

Conclusions. Household outweighs nosocomial transmission of ESBL producers. The effect of hospital infection

Hilty M: CID 2012

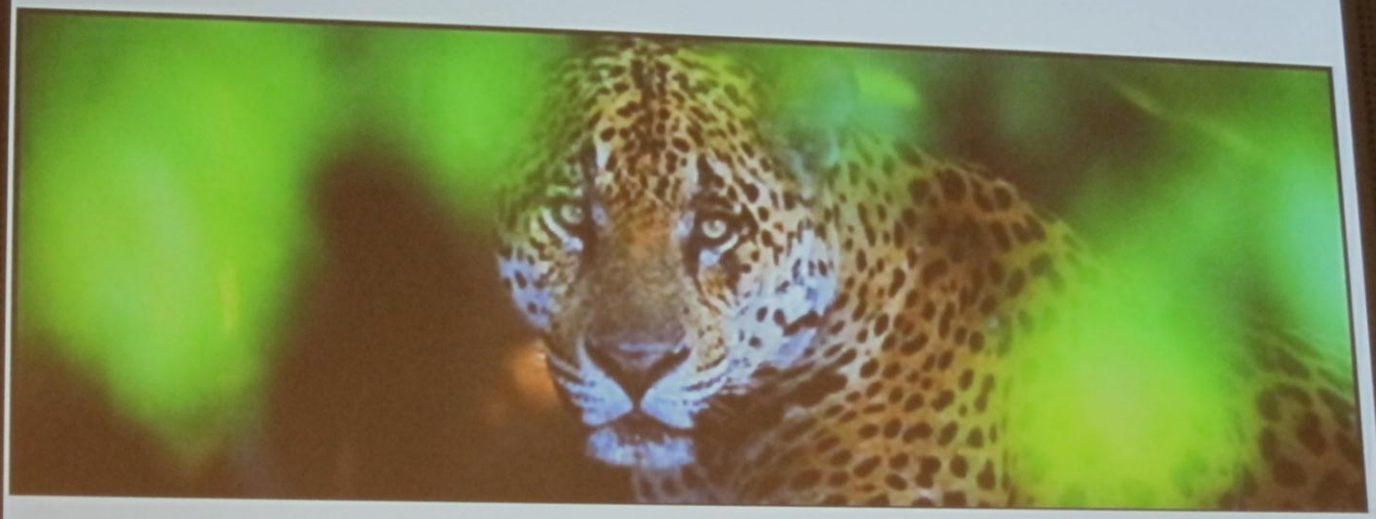
Vad lyfts i litteraturen - carbaNS Enterob.aceae

- Upptäck fallen inkl. bärare
- Obligatorisk rapport av fall
- Aktiv screening
  - utlandsvårdade
  - nyupptäckt tidigare okänd bärare

- Kohortvård med avdelad personal
- Nationell surveillance
- Nationell åtgärdsplan utformad

- Minska antibiotika överlag

Surveillance



If you can't see what's going on,
how can you control it?

ECCMID, Milan, 2011

Aktiv screening!

- Utlandsvård
  - jmfr MRSA
- Känd bärare återinläggs
- Överförs från sjukhus/äldre boende med känd smittspridning
- Läggs in på avdelning smittspridning får stora konsekvenser
  - Neonatal, IVA, hematologen etc
- Utlandsresenär → riskbedömning
- **feces/rectum**, sår, KAD-urin

Det är aldrig fel att screena en patient!

Vård av patient med ESBL-detta gäller alltid!

- tydlig journalanteckning, informera patienten om bärarskapet
- informera mottagande enhet om bärarskap vid förflyttning
- informera patienten om vikten av god handhygien, bistå vb
- serveras mat från buffé etc

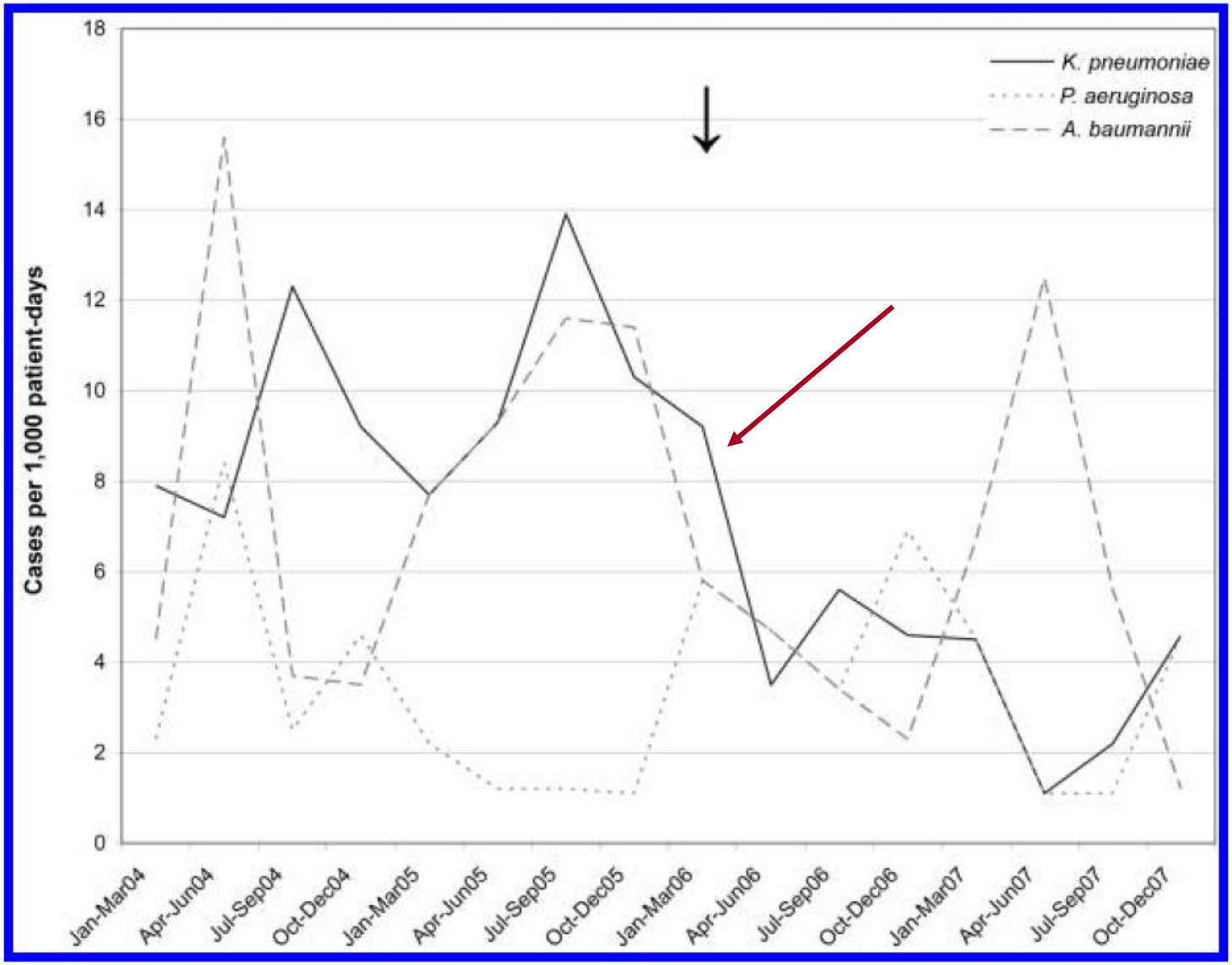
- bedöm utifrån patient och riskfaktorer för smittspridning

- odla alltid inför insättande av antibiotika

Patient som är aktuellt ESBL-pos.(Ent.acea)

- ESBL$_{A/M}$ i feces för övrigt “frisk”
  - basala hygienrutiner (enkelrum)
  - avdela/smittrena toalett
- ESBL$_{A/M}$ i någon lokal + riskfaktorer, särskilt diarré
  - eget rum med hygienutrymme en fördel
  - begränsa personal som utför patientnära moment (ej i mathantering)
  - serveras mat
- ESBL$_{CARBA}$
  - eget rum med hygienutrymme
  - äter och vistas på rummet
  - avdelad personal → begränsa personal/infektionsklinik

Aktiv surveillance och kohortvård
K. pneumoniae KPC



Kochar S, Infect Control Hosp Epidemiol 2009; 30:447-452

Kohortvård med avdelad personal var nödvändigt!

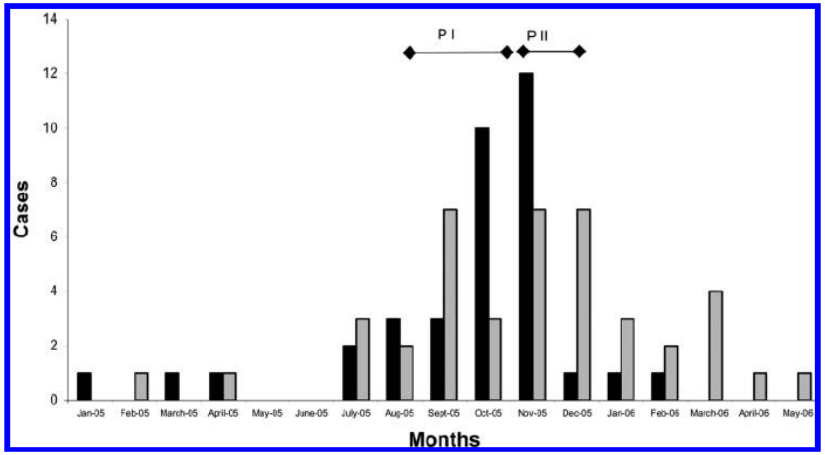


FIGURE 1. Epidemic curve of nosocomial extended-spectrum β-lactamase–producing *Klebsiella pneumoniae* cases in the intensive care units (ICUs) of a university hospital from January 2005 to May 2006. During the first period (P I), routine infection control measures were promoted; during the second period (P II), reinforced infection control measures were instituted. Black bars indicate nosocomial cases, and gray bars indicate imported cases.

Laurent C, ICHE, 2008
ESBL K. pn, ICU, Belgium

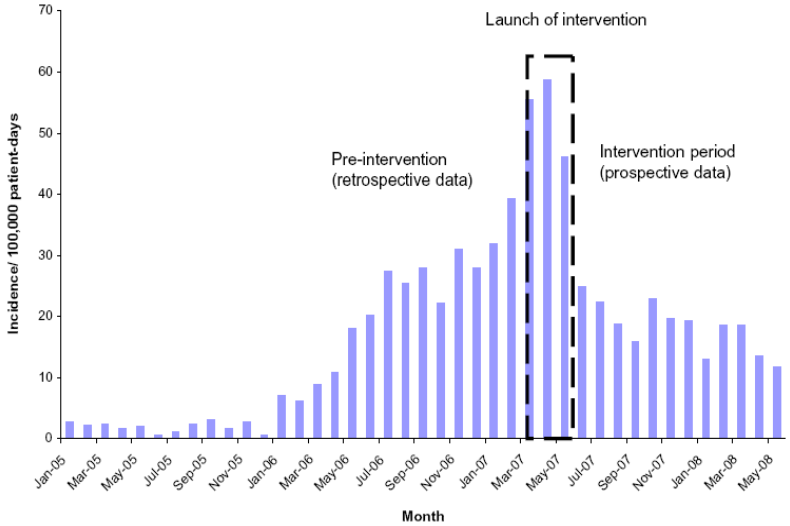


Figure 1. Monthly incidence of carbapenem-resistant Enterobacteriaceae detected by clinical culture per 100,000 patient-days, January 2005–May 2008. The intervention was gradually implemented nationwide from March through May 2007. Data through May 2007 were assembled retrospectively. Data from 1 June 2007 through 31 May 2008 were collected prospectively. The intervention led to a reduction in monthly incidence from a pre-intervention peak of 55.5 cases per 100,000 patient-days in March 2007 to 11.7 cases per 100,000 patient-days in May 2008 ($P < .001$).

Schwaber M, CID, 2011
KPC K. pn, country wide, Israel

Tidigare känd ESBLCARBA-bärare (Ent.acea) odlingsnegativ vid återinläggningsscreen

- vård
  - eget rum med hygienutrymme
  - äter och vistas på rummet
  - begränsa personalstaben → avdela vb utifrån riskfaktorer
  - kontakt med vårdhygien
  - fortsätt screena var 3:e dag och vid utskrift
    (om olika vårdrutiner för odlingspositiv och odlingsnegativ patient)

- Smittfriförklaras?????
  - Schechner V; ICHE, 2011 (Israel): 30 % pos >3 months
  - Zimmerman F; AmJIC, 2013: 387dgr. 39% pos >1 år

Nyupptäckt bärare ESBLCARBA

- Screena medpatienter upprepat tills inga nya fall upptäcks
- Överväg intagningsstopp vid oförklarad smittspridning
- Smittspårning mhj vårdhygien/smittskydd

Hur vet vi om vi har ett utbrott på g?

- Ha kunskap om den lokala epidemiologin (enzym, kloner etc)
- Kontinuerlig kontakt med laboratoriet – varslar vid misstanke!
- Bokför fall/vårdenhet

- **Polyklonala utbrott**
  - reagera på ESBL oberoende av bakterieart
  - flera olika isolat hos en pat.
  - notera, spara alla inte bara första isolatet

- Nationell övervakning

Table I

Epidemiological characteristics of 17 non-*Klebsiella pneumoniae* carbapenem-resistant Enterobacteriaceae (CRE) isolates identified during the programme period

Patient no.	Year	Ward	bla_{KPC}	bla_{KPC} allele	Isolate	Ertapenem MIC (μg/mL)	Imipenem MIC (μg/mL)	Additional CRE isolate
1	2008	Internal	+	2	*K. oxytoca*	8	16	-
2	2008	Internal	+	3	*E. coli*	8	16	-
3	2008	H/O	-	-	*E. cloacae*	8	16	-
4	2008	ICU	+	2	*E. coli*	8	16	-
5	2009	H/O	+	2	*E. coli*	4	16	*K. pneumoniae*
6	2009	H/O	+	3	*E. coli*	4	4	-
7	2009	H/O	+	2	*E. coli*	8	2	*K. pneumoniae*
8	2009	H/O	+	2	*E. coli*	8	8	-
9	2009	H/O	+	2	*E. aerogenes*	8	16	*K. pneumoniae*
10	2009	H/O	-	-	*E. cloacae*	8	8	-
11	2009	H/O	+	2	*E. cloacae*	8	8	*K. pneumoniae*
12	2009	H/O	+	2	*E. cloacae*	8	16	*K. pneumoniae*
13	2009	H/O	+	2	*E. cloacae*	8	16	*K. pneumoniae*
14	2009	H/O	+	2	*K. oxytoca*	8	16	-
15	2009	ICU	+	2	*E. cloacae*	8	16	*K. pneumoniae*
16	2009	ICU	+	2	*E. cloacae*	8	16	-
17	2009	ICU	+	2	*E. cloacae*	8	16	-

MIC, minimum inhibitory concentration; H/O, haematology/oncology; ICU, intensive care unit.

Geffen Y, J Hosp Infect 2010,

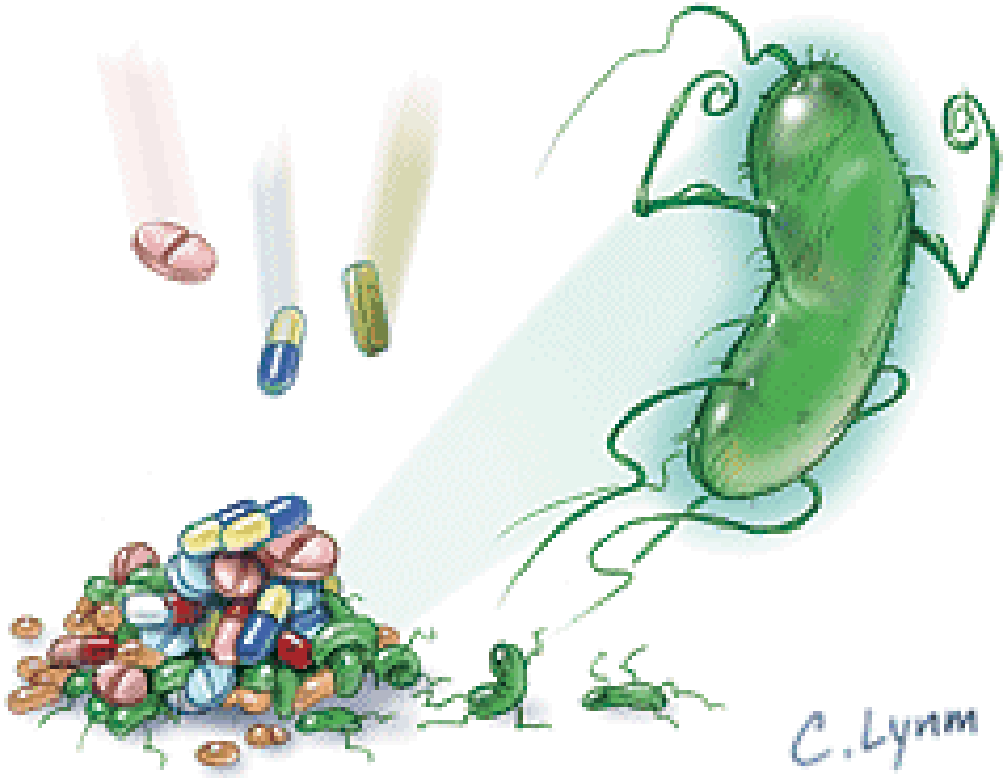
Vad kan vi göra innan det blir ännu värre?

- Vårdhygienisk standard på hög nivå
  - basala hygienrutiner: alltid!
  - minska VRI

- Minska fecal-oral smitta
  - handhygien patienter, besökare
  - inga buffér

- Vårdstrukturer
  - fler enkelrum med toaletter
  - patient-personal-kvot; överbeläggningar
  - allmän städning på hög nivå, toaletter
  - minska patientförflyttningar

Tack för ordet



Vem får det sista ……..