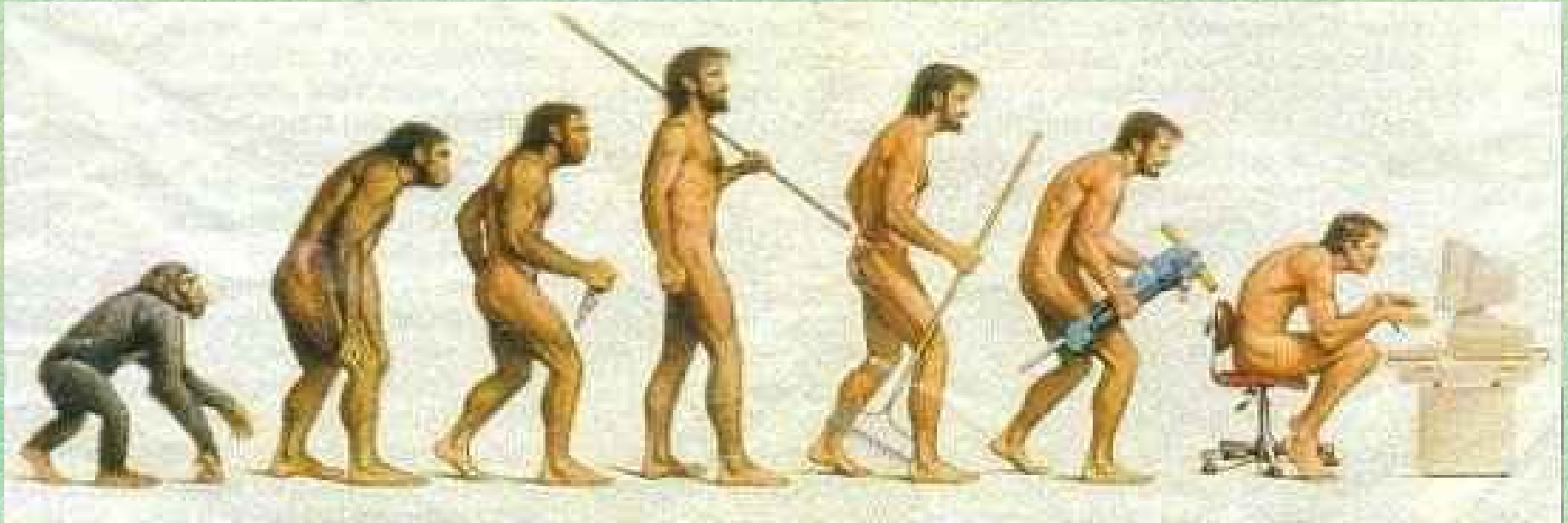


DTU meeting 16th March 2012

Combating ESBLs and carbapenemases

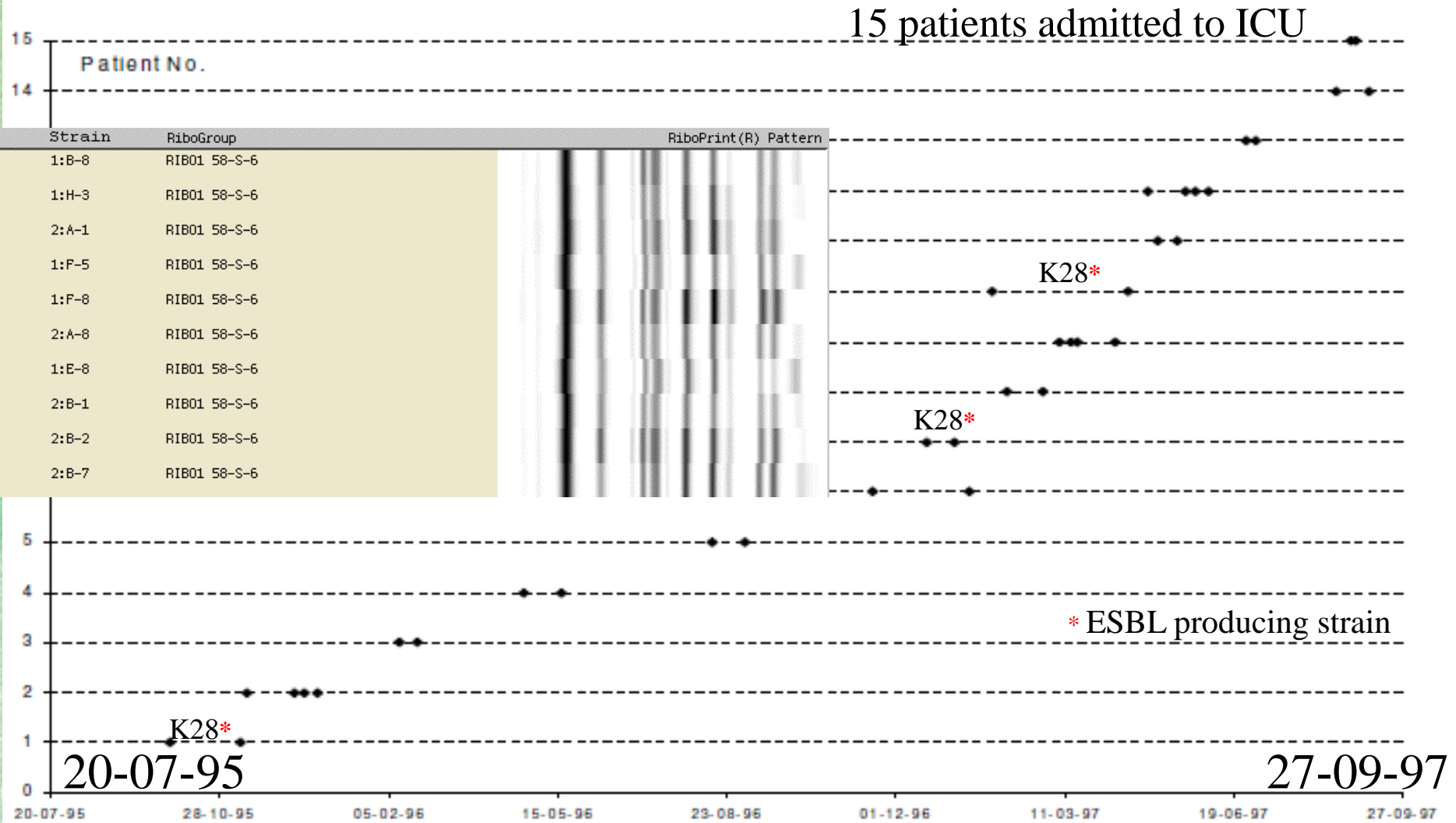


DSH 120312

ESBL in Denmark

- The two first cases were described in 1998
 - 1993. 75-year old female admitted to an ICU in Turkey after car accident. Prophylactic treatment with ceftazidime, vancomycin og tobramycine. Back in Denmark a K20 ESBL-producing (**SHV-5**) *K. pneumoniae* was found in an urine specimen.
 - 1996. 52-year old female admitted with secondary fecal peritonitis and MOF due to bowel perforation after bilateral ovarie-salpingectomy. From blood, urine, tracheal secretion and a CVK an ESBL-producing (**SHV-2**) *K. pneumoniae* was isolated.

A Two-year Lasting Outbreak of Multiple Antibiotic Resistant *K. pneumoniae* K28 in an Intensive Care Unit in Denmark



The prevalence of ESBL producing *E. coli* and *Klebsiella* strains in the Copenhagen area of Denmark in the period 1998 to 2003

| | Species | ESBL (N) | Prevalence of ESBL phenotype (%) | ESBL Genes (N) | | Prevalence of ESBL genes (%) |
|--|----------------------|-------------|--|-------------------|-----|------------------------------------|
| | | | | CTX-M | SHV | |
| 380 urine isolates March 2003 Hvidovre Hospital | <i>E. coli</i> | 3 | 0.8 | 2 | 1 | 0.8 |
| | <i>K. pneumoniae</i> | 0 | | | | |
| | <i>K. oxytoca</i> | 0 | | | | |
| 200 gentamicin R 1998 to 2003 Hvidovre Hospital | <i>E. coli</i> | 13 | 8.0 | 6 | 6 | 6.5 |
| | <i>K. pneumoniae</i> | 3 | | | 1 | |
| | <i>K. oxytoca</i> | 0 | | | | |
| 210 blood isolates Juli – Dec. 2001 Herlev Hospital | <i>E. coli</i> | 0 | 0 | | | 0 |
| 68 cefuroxime R Jan.02 - June 2003 Herlev Hospital | <i>E. coli</i> | 29 | 70.6 | 22 | 5 | 60.3 |
| | <i>K. pneumoniae</i> | 17 | | 13 | 1 | |
| | <i>K. oxytoca</i> | 2 | | | | |

SHV-2/-12 = 93% CTX-M gr.1 = 84%

National ESBL collection spring 2006

- Impression of an increase in number of ESBL-producers...
- Microbiologist were encouraged to send ind ESBL-producing isolates for characterization
- Overwhelmed by more than 600 isolates in a few months
- In a sample of the first 100 isolates:
 - 65 *E.coli*, 26 *K.pneumoniae*
 - 80 CTX-M (mostly CTX-M-15), few TEM and SHV ESBLs
 - Most isolates from a few large departments
- Skewed and no denominator

National prevalence of ESBL-producing enterobacteria 2007, 2009 and 2011

- All Dept. of clinical microbiology were invited
- Blood cultures, urines from hospital and GPs
- *E. coli*, *K. pneumoniae* and *P. mirabilis*
- Data on number of patients cultured, number of culture positive and number of ESBL-producers (screening and confirmatory positive)
- Collection of ESBL screening positive isolates for further characterization

DK prevalence of ESBL-producing enterobacteria 2007

Table V. Distribution of ESBL enzymes in 205 *Escherichia coli* isolates and 73 *Klebsiella pneumoniae* isolates (a *Proteus mirabilis* isolate producing CTX-M-15 is not shown).

| ESBL enzyme(s) in isolates | <i>E. coli</i> (<i>n</i> = 205) | <i>K. pneumoniae</i> (<i>n</i> = 73) |
|--|-------------------------------------|--|
| CTX-M-15 | 123 ^{a,b} | 15 |
| CTX-M-15 + SHV-28 | 0 | 25 |
| CTX-M-15 + SHV11, 32, 36, 38, 69, 83, or 85 | 0 | 16 ^b |
| CTX-M-14/18 | 24 ^a | 1 |
| CTX-M-14/18 + SHV-27 | 0 | 3 |
| CTX-M-1 | 22 | 0 |
| CTX-M-27 | 6 ^a | 0 |
| SHV-5/12 | 9 ^a | 4 |
| CTX-M-3 | 3 | 0 |
| CTX-M-9 | 3 | 0 |
| TEM-52 | 3 | 0 |
| CTX-M-57 | 2 | 0 |
| SHV-2 | 2 | 2 |
| AmpC + SHV-11 | 0 | 2 |
| Various CTM-X enzymes, alone or in combination ^c | 4 | 4 |
| ESBL phenotype (no genes found by PCR) | 4 ^b | 1 |

Hansen DS et al

SJID 2012; 44: 174-81

DK prevalence of ESBL-producing enterobacteria 2011

Data summary

- 12 of 13 clinical microbiology departments
 - \approx 95% of population
- October 2011
- 12.891 patients with blood cultures
- 36.764 patients with urine cultures
- **451** ESBL-producing isolates:
 - 348 *E. coli*
 - 101 *K. pneumoniae*
 - 2 *P. mirabilis*

DK prevalence of ESBL-producing enterobacteria 2011

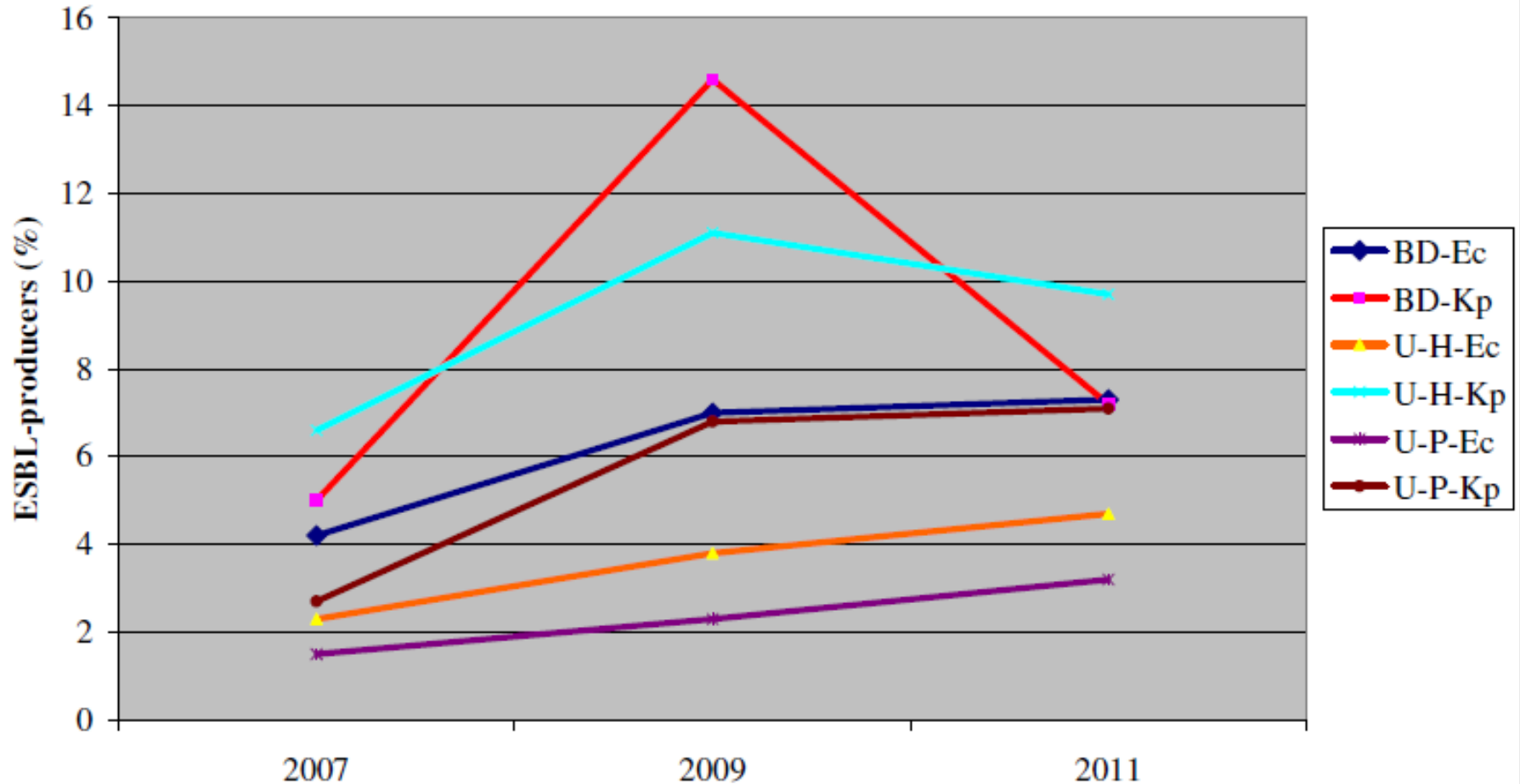
National prevalence of ESBL-producing *E. coli* and *K. pneumoniae* in 2007, 2009 and 2011, percentage increase and significance

| Species | % ESBL for each species and specimen | | | | | | |
|------------------------|--------------------------------------|------|------------|----------|------|-------------|---------|
| | 2007 | 2009 | % ↑ 2007-9 | P value* | 2011 | % ↑ 2009-11 | P value |
| Blood cultures | | | | | | | |
| <i>E.coli</i> | 4.2 | 7.0 | 67 | 0.052 | 7.3 | 4 | NS |
| <i>K.pneumoniae</i> | 5.0 | 14.6 | 192 | 0.0089 | 7.2 | -51 | NS |
| Urine, hospital | | | | | | | |
| <i>E.coli</i> | 2.3 | 3.8 | 65 | <0.0001 | 4.7 | 24 | 0.045 |
| <i>K.pneumoniae</i> | 6.6 | 11.1 | 68 | 0.0008 | 9.7 | -13 | NS |
| Urine, GP | | | | | | | |
| <i>E.coli</i> | 1.5 | 2.3 | 53 | 0.0065 | 3.2 | 39 | <0.009 |
| <i>K.pneumoniae</i> | 2.7 | 6.8 | 152 | 0.0038 | 7.1 | 4 | NS |

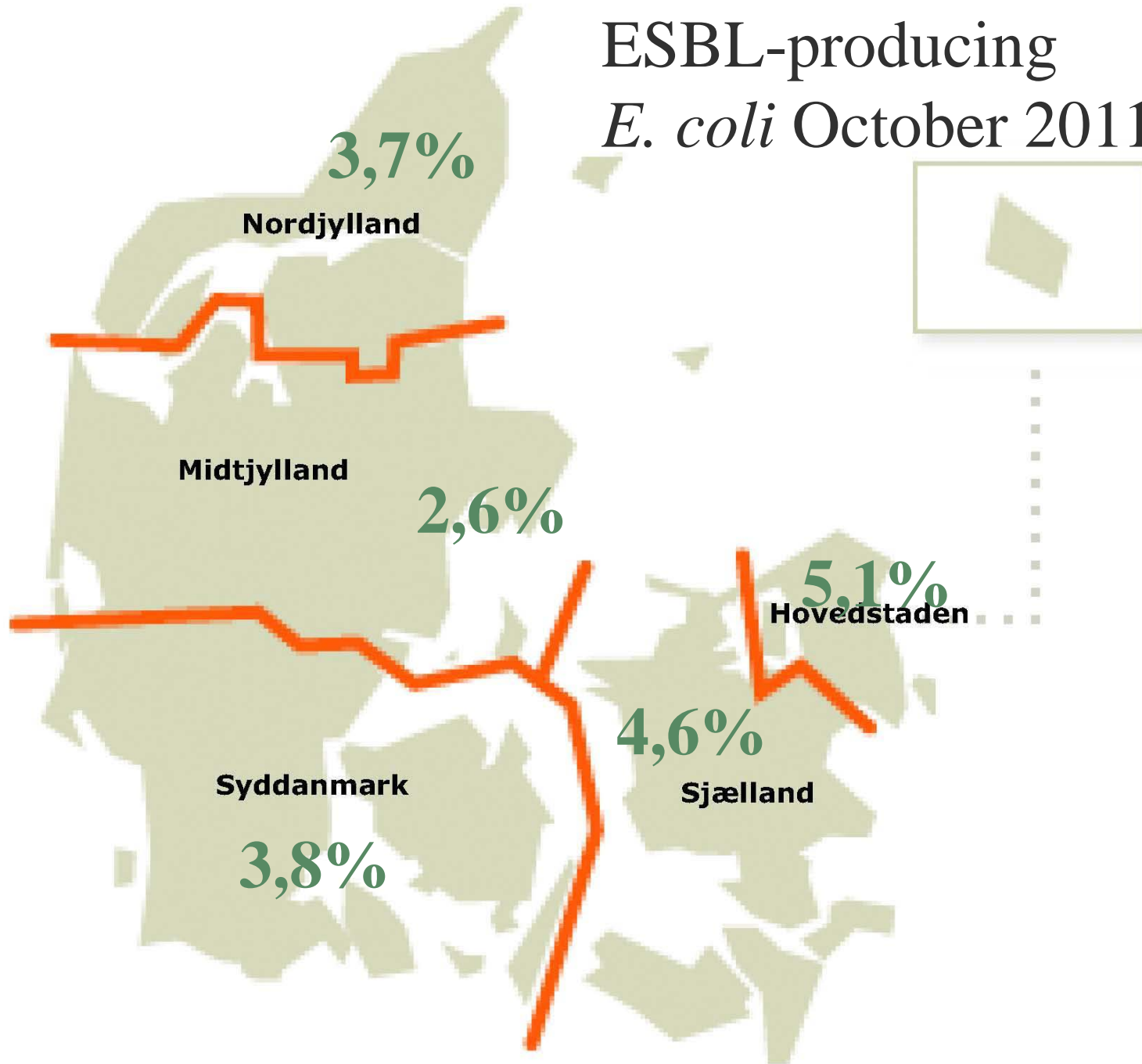
* X² two-tailed test

DK prevalence of ESBL-producing enterobacteria 2011

Prevalence of ESBL-producing *E. coli* and *K. pneumoniae* 2007-2011

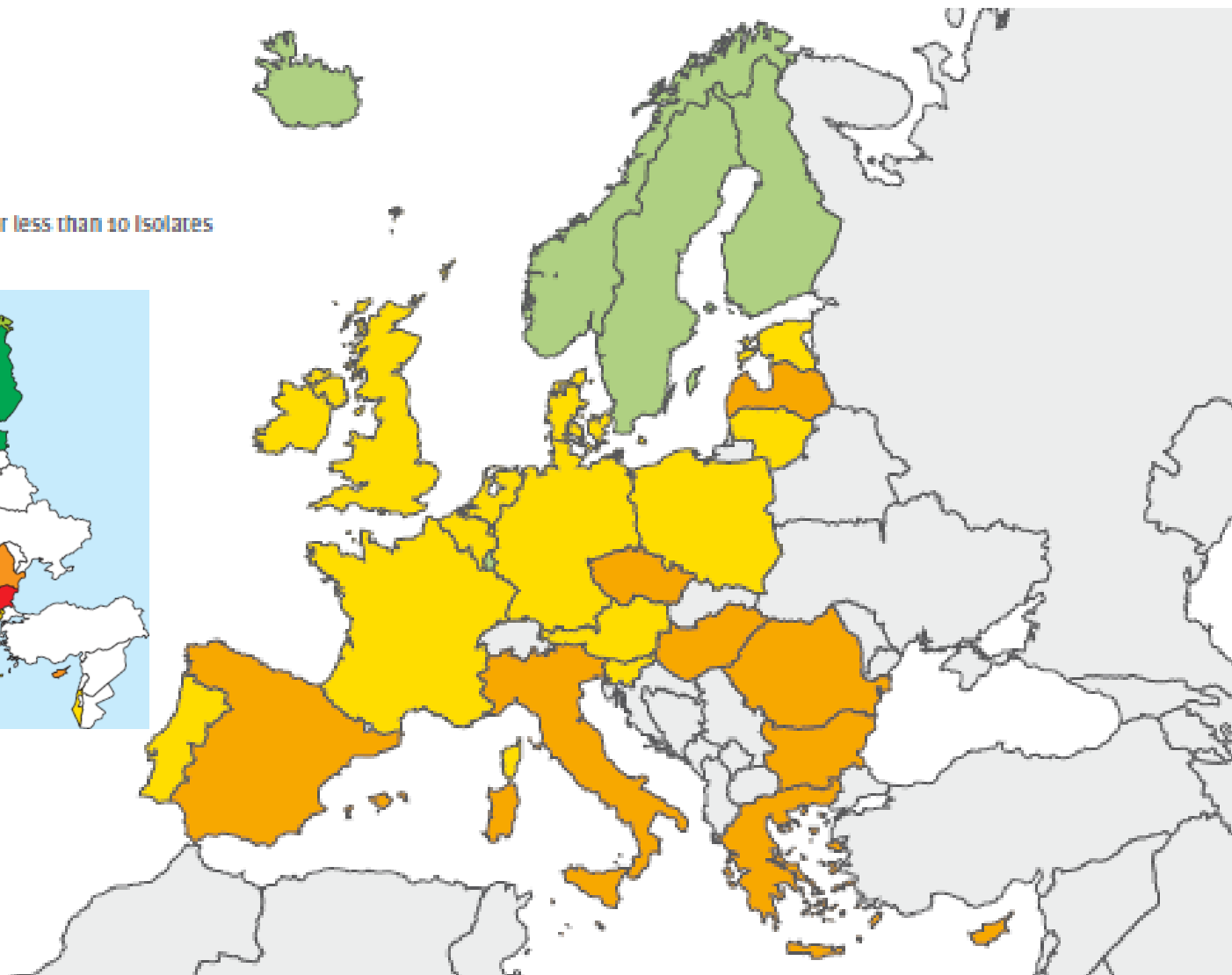


ESBL-producing *E. coli* October 2011



EARS 2010 – *E. coli*

Figure 5.14: *Escherichia coli*: proportion of invasive isolates with resistance to third-generation cephalosporins in 2010

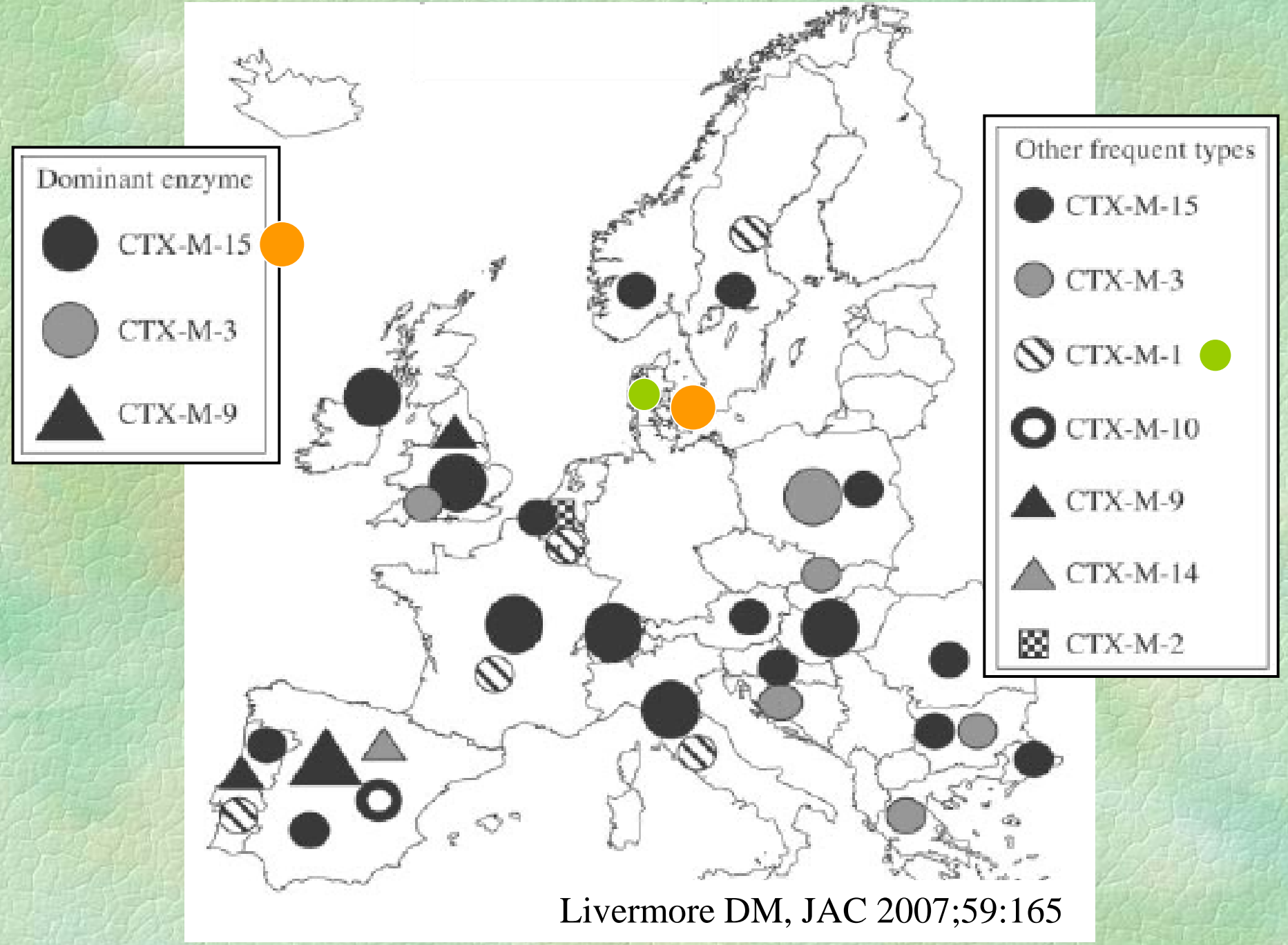


Non-visible countries

- Luxembourg
- Malta

DK prevalence of ESBL-producing enterobacteria 2009

| ESBL type | E.coli | K.pneumoniae | P.mirabilis | Antal |
|-------------------|---------------|---------------------|--------------------|--------------|
| CTX-M-15 | 105 | 10 | | 115 |
| CTX-M-15 + SHV-28 | 1 | 24 | | 25 |
| CTX-M-15 + SHV-32 | 1 | 14 | | 15 |
| CTX-M-15 + SHV-11 | | 9 | | 9 |
| CTX-M-1 | 19 | | 1 | 20 |
| CTX-M-14 | 15 | | | 15 |
| CTX-M-27 | 7 | | | 7 |
| CTX-M-3 | 4 | | | 4 |
| CTX-M +/- diverse | 7 | 13 | 1 | 21 |
| CIT/CMY-2/DHA | 6 | 1 | 1 | 8 |
| Ec pheno AmpC | 19 | | | 19 |
| KPC-2 + SHV-12 | | 1 | | 1 |
| SHV-2/5/11/12 | 3 | 6 | | 9 |
| TEM ESBL | 3 | | | 3 |
| ESBL phenotype | 8 | 1 | | 9 |
| ND | 5 | | | 5 |
| WT | 20 | 11 | | 31 |
| Hovedtotal | 223 | 90 | 3 | 316 |



Livermore DM, JAC 2007;59:165

DK prevalence of ESBL-producing enterobacteria 2009

| ESBL type | Eb | HI | Hn | Hlr | Nv | Ods | RH | SSI | VI | Vb | Åb | Åh | Total |
|-------------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|----------|-----------|-----------|-----------|-----------|------------|
| CTX-M 15 | 4 | 19 | 4 | 11 | 7 | 16 | 10 | 7 | 7 | 7 | 10 | 13 | 115 |
| CTX-M 1 | | 3 | 3 | 2 | 2 | 4 | | | 1 | | 3 | 2 | 20 |
| CTX-M 14 | | 1 | | 2 | 3 | 3 | | | | 1 | 5 | | 15 |
| CTX-M 27 | | | | 1 | 1 | | 2 | | | | | 3 | 7 |
| CTX-M + other | | 1 | 1 | 1 | 1 | 1 | | | 1 | | 3 | 1 | 10 |
| SHV 12 | | 1 | | | | | 2 | | | | | | 3 |
| TEM 52 | | | | | | 1 | | | | | | 1 | 2 |
| EC Pheno AmpC | 1 | 5 | | 2 | 2 | 5 | 1 | | | | 2 | 1 | 19 |
| CTI/CMY-2/DHA-1 | | 1 | | 2 | 1 | 1 | 1 | | | 1 | | 1 | 8 |
| CTX-M 15 + SHV-28 | ← | 5 | | 2 | 9 | | 6 | 2 | | | | 1 | 25 |
| CTX-M 15 + SHV-32 | ← | 3 | 1 | 1 | | 1 | 5 | | | | 1 | 3 | 15 |
| CTX-M 15 + SHV-11 | | | | | 2 | 1 | | | 1 | 1 | 2 | 2 | 9 |
| CTX-M + other | 3 | | 1 | | 4 | 2 | 1 | | | | 1 | | 12 |
| KPC-2 + SHV-12 | 1 | | | | | | | | | | | | 1 |
| SHV 2/5/11/12 | 1 | 1 | | 1 | 1 | 1 | | | | | 1 | | 6 |
| ESBL phenotype | 1 | 1 | 1 | 1 | | 3 | | | | | 1 | 2 | 10 |
| CTX-M 15 + other | | 1 | | | | 1 | 1 | | | | | | 3 |
| ND | 1 | | | 1 | 1 | 2 | | | | | | | 5 |
| WT | | 1 | 7 | 4 | 1 | 13 | 1 | | 1 | 1 | | 2 | 31 |
| Total | 12 | 43 | 18 | 31 | 35 | 55 | 30 | 9 | 11 | 11 | 29 | 32 | 316 |

January – December 2008, 80 3GC resistant isolates from blood

Table 1

Description of the 10 different pulsed-field gel electrophoresis (PFGE) clusters of extended-spectrum β -lactamase (ESBL)- or AmpC-producing resistant *Klebsiella pneumoniae* with more than one isolate per cluster.

| PFGE cluster | No. of isolates | MLST ^a | Phenotype | Genotype | % resistant isolates | | Region (province) |
|--------------|-----------------|-------------------|-----------|-------------------------|----------------------|------------|---|
| | | | | | Ciprofloxacin | Gentamicin | |
| 1 | 38 | ST15 | ESBL | CTX-M-15, SHV-28, TEM-1 | 100 | 86 | The Capital Region of Denmark (Zealand), The Zealand Region (Zealand), Region of Southern Denmark |
| 2 | 9 | ST16 | ESBL | CTX-M-15, SHV-1, TEM-1 | 100 | 0 | The Capital Region of Denmark (Zealand) |
| 3 | 5 | ST110 | ESBL | SHV-12 | 0 | 100 | The Zealand Region (Zealand), Central Denmark Region, North Denmark Region |
| 4 | 3 | ST11 | AmpC | DHA-1 | 100 | 0 | The Capital Region of Denmark, Central Denmark Region |
| 5 | 3 | ST70 | ESBL | CTX-M-15, SHV-32, TEM-1 | 100 | 100 | The Capital Region of Denmark, Central Denmark Region, North Denmark Region |
| 6 | 2 | ST473 | ESBL | CTX-M-14, SHV-11 | 50 | 100 | The Capital Region of Denmark, The Zealand Region (Zealand) |
| 7 | 2 | ST474 | ESBL | CTX-M-15, SHV-11, TEM-1 | 0 | 0 | Region of Southern Denmark |
| 8 | 2 | ST403 | ESBL | CTX-M-15, SHV-36, TEM-1 | 50 | 50 | Region of Southern Denmark, The Capital Region of Denmark (Zealand) |
| 9 | 2 | ST111 | ESBL | SHV-11, TEM-52 | 0 | 0 | Region of Southern Denmark |
| 10 | 2 | ST147 | ESBL | CTX-M-15, SHV-11, TEM-1 | 100 | 50 | North Denmark Region |

MLST, multilocus sequence typing.

^a MLST was performed on at least one isolate from each PFGE cluster.

Characterization of one year ESBL-producing *E.coli* isolates

- 1-year period (2008-9)
- 115 ESBL *E.coli* (115 pt.)
- 81% urine, 5% blood
- 68% hospital acquired
- 38% ST131 (hosp=com)
- 62% non-ST131
 - 31 O antigens
 - 28 K antigens
 - 20 H antigens

Table 2. ESBL genotypes of ST131 versus non-ST131 *E. coli* isolates among ESBL-producing *E. coli* from Copenhagen (2008-2009).

| ESBL genotype | total n=115 | ST131 n=44 | non-ST131 n=71 | P |
|---------------|----------------|---------------|-------------------|--------|
| CTX-M 15 | 52% | 80% | 35% | <0.001 |
| CTX-M 14 | 19% | 7% | 27% | 0.006 |
| CTX-M 1 | 13% | 0% | 18% | 0.002 |
| CTX-M 27 | 6% | 9% | 3% | NS |
| Non-Typable | 3% | 0% | 4% | NS |
| SHV-12 | 2% | 0% | 3% | NS |
| TEM-12 | 2% | 0% | 3% | NS |
| CTX-M 2 | 1% | 2% | 0% | NS |
| CTX-M 3 | 1% | 2% | 0% | NS |
| CTX-M 55 | 1% | 0% | 1% | NS |
| CTX-M 8 | 1% | 0% | 1% | NS |
| CTX-M 9 | 1% | 0% | 1% | NS |
| SHV-new | 1% | 0% | 1% | NS |
| TEM-52 | 1% | 0% | 1% | NS |

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