

# Transmission Dynamics of Extended-Spectrum $\beta$ -lactamase–Producing Enterobacteriaceae in the Tertiary Care Hospital and the Household Setting

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**Background.** Studies about transmission rates of extended-spectrum  $\beta$ -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*<sub>ESBL</sub> 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 control measures may differ between different species and clones of ESBL producers.

Since the late 1980s, extended-spectrum  $\beta$ -lactamase (ESBL)–producing Enterobacteriaceae, mainly *Klebsiella*

*pneumoniae*, have been recognized as a major cause of nosocomial infections and outbreaks [1]. However, during the late 1990s, *bla*<sub>ESBL</sub> genes have increasingly been identified within the community setting in the context of urinary tract infections (UTIs) caused by *Escherichia coli* [2, 3]. Currently, the CTX-M-15 is recognized as the most widely distributed *bla*<sub>ESBL</sub> among Enterobacteriaceae [4, 5], and the worldwide spread of the *E. coli* hyper-epidemic clone of sequence type (ST) 131 represents one of the major challenges for the healthcare systems [6, 7].

An important strategy for controlling the spread of these multidrug-resistant pathogens is the identification of patients with risks for acquisition [2, 8]. In addition, active surveillance and isolation precautions are recommended (<http://www.premierinc.com/safety/topics/guide>

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lines/cdc\_guidelines.jsp). However, proposed guidelines refer to the outbreak situations only and data about the efficiency of infection control measures in the endemic hospital setting or even in the community are currently not available [9, 10].

Community spread of ESBL producers indicates that person-to-person transmission may occur outside the hospital but data regarding household spread and risk factors thereof are still limited [11, 12]. Prolonged carriage of ESBL producers in the gastrointestinal tract of patients after hospital discharge may enhance such transmission [13]. Thus, a better understanding of the transmission dynamics of ESBL producers in this setting is warranted in order to guide measures for the control of ESBL producers in the community.

In the present study, we prospectively evaluated transmission rates of ESBL-producing *E. coli* (ESBL-*Ec*) and ESBL-producing *K. pneumoniae* (ESBL-*Kp*) from hospital index patients to hospital roommates and to household persons. Our data indicate that the transmission rate is significantly higher within households than in our non-outbreak hospital scenario.

## METHODS

### Study Setting and Recruitment of Patients

A prospective, longitudinal study was conducted from 1 May 2008 through 30 September 2010. Index patients and their hospital contacts were recruited from 1 May 2008 through 30 September 2009 at the University Hospital of Bern (Bern, Switzerland), a 1033-bed tertiary-care hospital with a 30-bed mixed intensive care unit (ICU), and more than 35 000 admissions resulting in 280 000 patient-days per year. Index patients included pediatric (age, <10 years) and adult patients hospitalized or treated as outpatients at the study center presenting with a newly detected carriage or infection with ESBL-*Ec* or ESBL-*Kp*. The study was conducted in accordance with local requirements of the ethics committee.

### Definitions

Patients were categorized as *inpatients* if they required admission to the hospital for >24 hours. An *index patient* was defined as an inpatient or outpatient with a newly recognized infection or colonization with ESBL-*Ec* or ESBL-*Kp* isolates. *Hospital contact patients* were defined as roommates who shared the same wardroom, ICU room, or immediate care room for  $\geq 48$  hours with an index patient. *Household contact persons* were defined as persons who shared the same household with the index patient on a regular basis. *Transmission* was assumed when the index patient and contacts shared a clonally-related (see below) ESBL-*Ec* or ESBL-*Kp* isolate with identical *bla*<sub>ESBL</sub> gene(s).

### Data Collection

For inpatients and outpatients included in the study, the presence of the following risk factors for ESBL carriage active during the previous 3 months were considered: previous hospitalization, ICU stay, surgical procedures, use of indwelling devices (ie, intravascular and urinary catheters, endotracheal and naso-gastric tubes, tracheostomy, and drainages), peritoneal- or hemodialysis, urinary or fecal incontinence, recurrent UTI, intermittent self-catheterization or other chronic urologic conditions, presence of skin lesions, domestic or livestock animal husbandry, antibiotic treatment, immunosuppressive therapy (ie,  $\geq 20$  mg/d of prednisone, radiotherapy, chemotherapy, or immunomodulators). The presence and severity of comorbidity was assessed at recruitment by calculating the Charlson comorbidity index [14]. The patient setting (eg, long-term care facility, acute care hospital, or private household) was recorded at recruitment (see below).

### Infection Control Policy

According to local infection control guidelines, patients with ESBL carriage were put in contact isolation if they presented with any of the above-mentioned risk factors. The isolation protocol involved use of gloves by medical personnel during any physical contact and medical procedure. Occupation of a 2-bed room was possible if the neighboring patient did not present any of these risk factors (which are assumed to enhance the risk of transmission). For ICU patients, isolation measures were implemented in 4-bed rooms. Hospital-wide hand hygiene compliance is monitored on a yearly basis since 2005 using the SwissNOSO methodology. Overall, compliance was 62% in 2008, 63% in 2009, and 68% in 2010 (<http://www.swissnoso.ch>).

### Screening and Follow-up Program

The follow-up period for inpatients and outpatients and their contacts was 12 months except for death or stay abroad. For index inpatients, screening samples were obtained at time of first detection of the ESBL-producing organism and weekly thereafter until hospital discharge. After discharge of the index patient, samples were also collected from the household contact persons at 3-month intervals. Screening samples included a fecal sample and, for index patients only, urine samples in the case of a Foley catheter, respiratory samples in case of intubation or tracheostomy and, if applicable, drainage fluid samples and swabs from skin lesions. Screening was stopped if the index patient and his or her household contacts tested negative in 2 consecutive screenings. For index outpatients, a fecal sample was obtained at time of first detection of the ESBL producer and trimonthly thereafter. In addition, screening samples were obtained in case of hospitalization at the study center during the follow-up period. Hospital contact

patients were screened weekly until 1 week after physical separation from the index patient and at hospital discharge if the last screening was performed >7 days before discharge.

### Detection and Phenotypic Analysis of Isolates

Stool samples were analyzed with different selective culture media designed to detect cephalosporin-resistant isolates: ChromID ESBL agar, BLSE agar, a bi-plate with 2 selective media (MacConkey agar plus ceftazidime and Drigalski agar plus cefotaxime at a concentration of 2 and 1.5 mg/L, respectively), and CHROMagar ESBL. Growing colonies were subject to species identification by use of standard biochemical methods and the Vitek 2 system. Phenotypic confirmation of ESBL production was obtained by using the double-disk synergy test with ceftazidime, cefpodoxime, and aztreonam in combination with amoxicillin-clavulanate [15]. Coresistance to other antibiotics was assessed by disk diffusion and interpreted according to the Clinical Laboratory Standards Institute criteria [16]. Multidrug-resistant isolates were resistant to at least 1 representative of  $\geq 3$  antimicrobial classes as described elsewhere [6].

### Molecular Characterization of ESBL-Producing Isolates

Polymerase chain reaction (PCR) for *bla*<sub>TEM</sub> and *bla*<sub>SHV</sub> genes was performed as reported elsewhere [17, 18]. For *bla*<sub>CTX-M</sub> genes, universal primers were used as an initial screen revealing the distinct CTX-M groups 1, 2, and 4 [19]. Subsequently, *bla*<sub>CTX-M</sub> group specific primers were used for amplification and sequencing CTX-Ms of group 1 (CTX-M\_F\_Grp1, TGG TTAATAAATCACTGCGYCA; CTX-M\_R\_Grp1, GTYGGT GACGATTTTAGCC; CTX-M\_R2\_Grp1, ACAGAYTCGGTT CGCTTCA), group 2 (CTX-M\_F\_Grp2, AATGTAAACGGT GATGGCGA; CTX-M\_R\_Grp2, GATTTTCGCCGCCGCA), and group 4 (CTX-M\_F\_Grp4, AGAGARTGCAACGGAT GATGT; CTX-M\_R\_Grp4, CCCYTYGGCGATGATTCTC; CTX-M\_F2\_Grp4, CAGACGTTGCGTCAGCTTAC).

DNA sequencing was done according to the manufacturer's instructions using the ABI 3130 sequencer. Sequences were analyzed using MEGA 4 [20], translated into protein sequences, and compared with those previously described (<http://www.lahey.org/Studies/>). Two new TEM types were identified (ie, TEM-191 and TEM-192; accession numbers JF949915 and JF949916, respectively).

### Analysis of Clonal Relatedness

Phylogenetic groups (ie, A, B1, B2, and D) of ESBL-*Ec* were determined as reported elsewhere [21]. Multilocus sequence typing for selected ESBL-*Ec* and ESBL-*Kp* isolates was performed according to the Achtman and Pasteur schemes, respectively [22, 23]. Furthermore, all ESBL-*Ec* of phylogenetic

group B2 were tested for the *pabB* allele to detect those of ST131 according to the Achtman scheme [24].

The relatedness of ESBL-*Ec* and ESBL-*Kp* isolates was also analyzed by pulse-field gel electrophoresis (PFGE) using the *XbaI* restriction enzyme and the repetitive extragenic palindromic PCR (rep-PCR) [25, 26]. Resulting rep-PCR and PFGE fingerprints were analyzed using bioanalyzer and GEL-COMPAR II software. The cosine coefficient and unweighted pair group method with arithmetic means was used for cluster analysis. ESBL-*Ec* isolates were defined as clonally-related when they shared the same phylogenetic group, >85% genetic relatedness by rep-PCR and similar PFGE band patterns as defined by the Tenover criteria (ie, differing by  $\leq 3$  bands) [26]. Clonally-related ESBL-*Kp* isolates were defined as those of ESBL-*Ec* but the rep-PCR cutoff was >90%.

### Statistical Analysis

Using STATA version 10, continuous and categorical variables were tested by the Student *t* test and the Fisher exact test (2-tailed), respectively. Kaplan-Meier curves were derived by Prism software and differences calculated using the log-rank test.

## RESULTS AND DISCUSSION

### Molecular Characteristics and Antibiotic Resistance Patterns of ESBL-Producing Isolates of Index Patients

A total of 82 index patients (48 inpatients and 34 outpatients) with an infection or colonization due to ESBL-*Ec* ( $n = 72$ ) or ESBL-*Kp* ( $n = 10$ ) were included into the study (Table 1). New index cases were detected with a median frequency of 4.8 (range, 1–9) patients per month but there was no outbreak situation (Figure 1). The mean incidence of index inpatients was 0.12 cases per 1000 patient-days (48 index inpatients for a total of 400 000 patient-days) in accordance with a recent German study in which an incidence of 0.12 cases per 1000 patient-days was observed [27].

Overall, the CTX-M-15 producers were the most prevalent ESBL-*Ec* ( $n = 42$ ) and ESBL-*Kp* ( $n = 7$ ) isolates (Table 1). ESBL-*Ec* clustered mainly within phylogenetic groups A, B2, and D. Twenty (28%) isolates were of ST131 according to the Achtman scheme (Table 1). Presence of *bla*<sub>CTX-M-15</sub> was associated with resistance to ciprofloxacin and gentamicin ( $P < .001$  and  $P < .001$ , respectively). As previously observed, ciprofloxacin resistance was highly prevalent among ESBL-*Ec* of ST131 [6].

### Characteristics of Index Patients and Sampling of ESBL-Producing Isolates

As shown in Table 2, 13% of index patients were children. An earlier Swiss study had already indicated that this population

**Table 1. Molecular Characteristics and Antibiotic Resistance Patterns of Extended-Spectrum  $\beta$ -Lactamase-Producing *Escherichia coli* and *Klebsiella pneumoniae* Isolates**

Parameter	Species and Phylogenetic Group, No. (%)							Total
	<i>Ec</i> A	<i>Ec</i> B1	<i>Ec</i> B2 ( <i>pabB</i> <sup>-</sup> )	<i>Ec</i> B2 ( <i>pabB</i> <sup>+</sup> ) <sup>a</sup>	<i>Ec</i> D	<i>Ec</i> (all)	<i>Kp</i> (all)	
Total	21	7	3	20	21	72	10	82
ESBL genes								
<i>bla</i> <sub>CTX-M-1</sub>	4 (19)	1 (14)	0 (0)	0 (0)	1 (5)	6 (8)	0 (0)	6 (7)
<i>bla</i> <sub>CTX-M-14</sub>	1 (5)	0 (0)	0 (0)	3 (15)	3 (14)	7 (10)	1 (10)	8 (10)
<i>bla</i> <sub>CTX-M-15</sub>	12 (57)	2 (29)	1 (33)	14 (70)	13 (62)	42 (58)	6 (60)	48 (59)
<i>bla</i> <sub>CTX-M-15</sub> and <i>bla</i> <sub>SHV-5</sub>	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	1 (1)
<i>bla</i> <sub>CTX-M-27</sub>	0 (0)	1 (14)	0 (0)	1 (5)	1 (5)	3 (4)	0 (0)	3 (3)
<i>bla</i> <sub>SHV-2/-2A/-5/-12</sub>	1 (5)	0 (0)	1 (33)	1 (5)	0 (0)	3 (4)	2 (20)	5 (6)
Other	1 (5)	3 (43)	1 (33)	1 (5)	2 (10)	8 (11)	0 (0)	8 (10)
Unknown <i>bla</i> <sub>ESBL</sub>	2 (10)	0 (0)	0 (0)	0 (0)	1 (5)	3 (4)	0 (0)	3 (4)
Resistance phenotype <sup>b</sup>								
Gentamicin	8 (38)	2 (29)	2 (67)	11 (55)	13 (62)	36 (50)	10 (100)	46 (56) <sup>c</sup>
Ciprofloxacin	15 (71)	4 (57)	0 (0)	17 (85)	12 (57)	48 (67)	8 (80)	56 (68) <sup>d</sup>
Trimethoprim-sulfamethoxazole	17 (81)	6 (86)	2 (67)	12 (60)	17 (81)	54 (75)	9 (90)	63 (77)
Piperacillin-tazobactam	10 (48)	2 (29)	0 (0)	5 (25)	1 (5)	18 (25)	7 (70)	25 (30)
MDR isolates <sup>e</sup>	10 (48)	3 (43)	0 (0)	9 (45)	7 (33)	29 (40)	9 (90)	38 (46)

Abbreviations: *Ec*, *Escherichia coli*; ESBL, extended-spectrum  $\beta$ -lactamase; *Kp*, *Klebsiella pneumoniae*; MDR, multidrug-resistant.

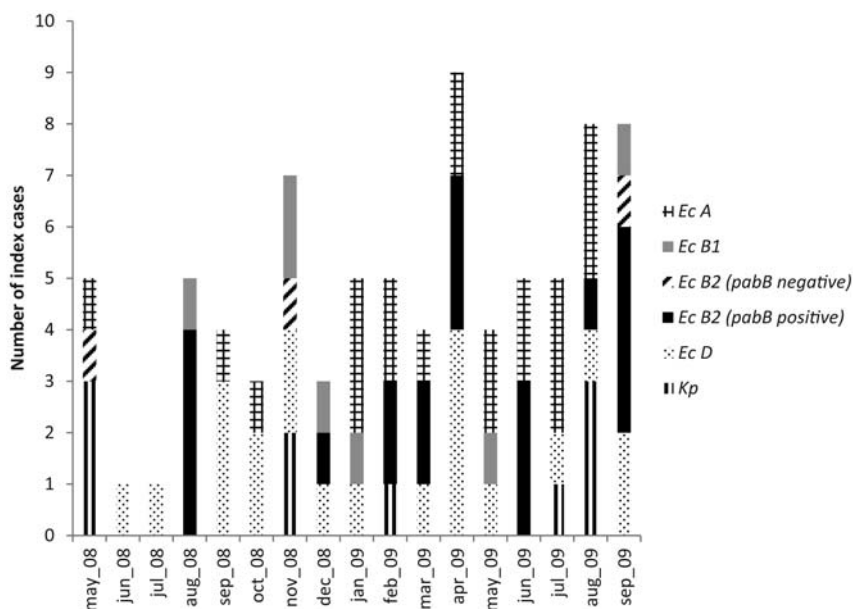
<sup>a</sup> Phylogenetic group B2 with *pabB* gene are indicative for sequence type 131 according to the Achtman multilocus sequence typing scheme.

<sup>b</sup> Intermediate susceptibility was grouped as resistant.

<sup>c</sup> Thirty-six of 46 isolates carried *bla*<sub>CTX-M-15</sub> ( $P < .001$ ).

<sup>d</sup> Forty-one of 56 isolates carried *bla*<sub>CTX-M-15</sub> ( $P < .001$ ).

<sup>e</sup> MDR isolates were resistant to at least 1 representative of  $\geq 3$  antimicrobial classes as described elsewhere [6].



**Figure 1.** Number of new patients with extended-spectrum  $\beta$ -lactamase-producing *Klebsiella pneumoniae* or *Escherichia coli* isolates detected from May 2008 through September 2009. Data on *E. coli* are stratified according to the phylogenetic groups A, B1, B2, and D. *E. coli* isolates of group B2 which are positive for the *pabB* gene are indicative for sequence type 131 according to the Achtman multilocus sequence typing scheme [24]. Abbreviations: *Ec*, *Escherichia coli*; *Kp*, *Klebsiella pneumoniae*.

**Table 2. Characteristics of the 82 Index Patients Carrying Extended-Spectrum  $\beta$ -Lactamase-Producing Isolates**

Parameter	Value for Index Patients (n = 82)	
	Outpatients	Inpatients
Total	34	48
Age in years, mean $\pm$ SD	39.8 $\pm$ 23.3	58.2 $\pm$ 21.5
<10	7	4
10–50	14	5
>50	13	39
Female, No. (%)	29 (85)	23 (48)
Charlson score, mean $\pm$ SD	1.0 $\pm$ 2.3	3.0 $\pm$ 2.7 <sup>a</sup>
Charlson score, age adjusted, mean $\pm$ SD	1.7 $\pm$ 2.6	4.7 $\pm$ 3.3 <sup>a</sup>
Referred from, No. (%)		
Household	34 (100)	25 (52)
Other hospital	0 (0)	11 (23)
Long-term care facility	0 (0)	4 (8)
Other	0 (0)	4 (8)
Unknown	0 (0)	4 (8)
Type of sample with ESBL producer detected, No. (%)		
Urine	32 (94)	27 (56)
Blood culture	0 (0)	5 (10)
Tracheal aspirates	0 (0)	3 (6)
Wound	0 (0)	4 (8)
Feces	0 (0)	2 (4)
Other	2 (6)	7 (15)
Antibiotic exposure during the 3 months before referring to hospital, No. (%)		
Yes	30 (88)	39 (81)
No	2 (6)	0 (0)
Unknown	2 (6)	9 (19)
Antibiotic treatment at sampling date, No. (%)		
Yes	14 (41)	32 (67)
No	15 (44)	5 (10)
Unknown	5 (15)	11 (23)
Bacterial species with ESBLs, No. (%)		
<i>Escherichia coli</i>	32 (94)	40 (83)
<i>Klebsiella pneumoniae</i>	2 (6)	8 (17)
Initial screening of stool samples, No. (%)		
ESBL producer of the identical species <sup>b</sup>	22 (65)	34 (71)
ESBL producer of different species <sup>b</sup>	0 (0)	5 (10)
No ESBL producers detected	10 (29)	7 (15)
No initial screening done	2 (6)	2 (4)

Abbreviations: ESBL, extended-spectrum  $\beta$ -lactamase; SD, standard deviation.

<sup>a</sup> Data were not available for 3 index patients.

<sup>b</sup> When compared with the first ESBL-producing isolate.

may be an important reservoir of ESBL producers [28]. In accordance with the literature, the urinary tract was the most frequent source of ESBL producers [2]. Index inpatients had more severe underlying disease and were more frequently referred from a hospital setting compared with the index outpatients. Almost all index patients had received antibiotic treatment during the 3 months prior to the detection of ESBL producers (Table 2).

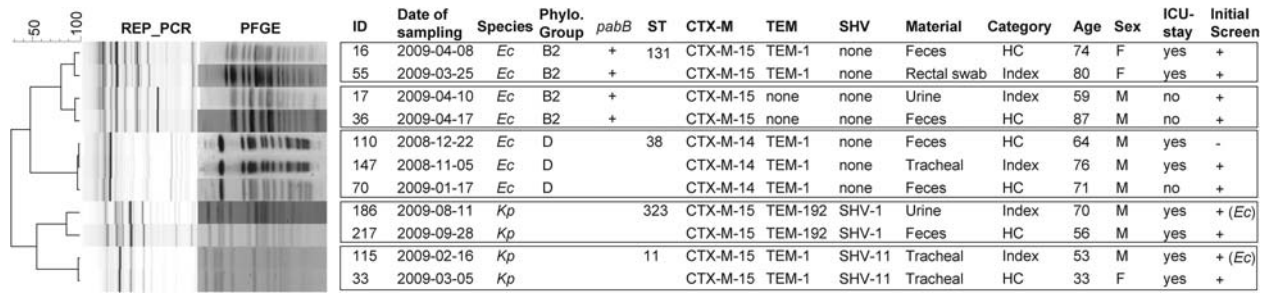
The mean ( $\pm$  SD) time between collection of the initial sample and the first screening was 18.4 days ( $\pm$  29.7). Fecal carriage of an identical ESBL producer as found in the clinical sample was detected in the initial screening in 65% of outpatients and 71% of inpatients, which is comparable with a previous study [11]. Index inpatients stayed in the hospital for a mean ( $\pm$  SD) of 34.6 days ( $\pm$  37.1). Carriage of an ESBL producer was detected within 48 hours after hospital entry in 20 (42%) of the index inpatients (data not shown).

### Transmission Dynamics in the Hospital

A total of 88 hospital patients were exposed for 715 days to the 40 index in patients with ESBL-*Ec* for a mean ( $\pm$  SD) of 8.1 days ( $\pm$  5.8). The mean ( $\pm$  SD) follow-up time of the hospital contacts was 27.6 days ( $\pm$  40.0). An ESBL-*Ec* was found in 9 of 88 (10.2%) contact patients (Supplementary Figure 1). According to the study definition, transmission from the index patient was assumed for 4 contacts (ie, patients 36, 16, 110, and 70; Figure 2). The overall transmission rate for ESBL-*Ec* was therefore 4.5% (4 of 88 exposed contacts), corresponding to an incidence of transmission of 5.6 cases per 1000 exposure days. The observed transmission rates were consistent with a report with a transmission rate of 2.8% and 4.2 cases per 1000 exposure days [29].

A total of 24 hospital patients were exposed to the 8 index in patients with ESBL-*Kp* during 144 days for a mean ( $\pm$  SD) of 6.0 days ( $\pm$  4.3). ESBL-*Kp* was found in 7 of 24 (29.1%) hospital contacts (Supplementary Figure 1) but transmission was plausible for only 2 contacts (8.3%; incidence, 13.8 cases per 1000 exposure days; Figure 2). Therefore, the transmission rate was higher for ESBL-*Kp* (8.3%) than for ESBL-*Ec* (4.5%), albeit the difference did not reach statistical significance. However, the incidences of ESBL-*Ec* (5.6 cases per 1000 exposure days) and ESBL-*Kp* (13.8 cases per 1000 exposure days) transmission resulted in a significantly higher incidence of ESBL-*Kp* transmission ( $P < .0001$ ). This suggests that ESBL-*Kp* has a higher transmission potential than ESBL-*Ec*, in accordance with the frequency of ESBL-*Kp* nosocomial outbreaks being reported in the literature (Supplementary Data). Notably, the ESBL-*Kp* STs involved in transmission events were ST11 and ST323, which have been identified as frequently detected clones also carrying *bla*<sub>KPC</sub> [30].





**Figure 2.** Characteristics of hospital transmissions from index patients to hospital contacts of extended-spectrum beta-lactamase (ESBL)-producing *Klebsiella pneumoniae* and *Escherichia coli*. Sequence types (ST) are shown according to Pasteur (*K. pneumoniae*) and Achtman (*E. coli*) multilocus sequence typing (MLST) scheme. Furthermore, *E. coli* isolates of group B2 that are positive for the *pabB* gene are indicative for ST131 according to Achtman MLST scheme. Initial screening of feces samples revealed identical results for 8 patients. For the remaining, 2 ESBL-producing *E. coli* instead of initial ESBL-producing *K. pneumoniae* were detected (ie, index patients 186 and 115), whereas 1 negative stool sample results was obtained (ie, patient 110). Abbreviations: *Ec*, *Escherichia coli*; HC, hospital contact; ICU, intensive care unit; *Kp*, *Klebsiella pneumoniae*; PFGE, pulse-field gel electrophoresis; rep-PCR, extragenic palindromic polymerase chain reaction; ST, sequence type.

### Effect of Isolation Precautions in the Hospital

Most of the index patients with ESBL-*Ec* (75%) were not under isolation precautions during exposure of the contacts (537 of 715 exposure days). In contrast, only 22% of ESBL-*Kp* index patients (32 of 144 exposure days) were not in isolation ( $P < .001$ ). Therefore, one might have expected a higher transmission rate for ESBL-*Ec* than ESBL-*Kp*, whereas the opposite was observed, in agreement with a higher transmission potential of ESBL-*Kp* as discussed above. However, the interpretation of this result requires some caution. In this study, index patients were only isolated if they had risk factors for transmission. Therefore, index patients with ESBL-*Kp* were likely more prone to serve as a source of transmission than index patients with ESBL-*Ec*. Furthermore, ESBL-*Kp*-colonized index patients were more often in the ICU for at least 1 day ( $n = 4$ ; 50%) than the ESBL-*Ec*-colonized index patients ( $n = 11$ ; 27.5%) and might therefore have been undergoing more clinical procedures leading to transmission.

### Transmission Dynamics in the Household Setting

ESBL-*Ec* carriage was found in 31 (35.2%) of 88 household contacts, but based on the molecular analysis, transmission was plausible for only 20 (22.7%) contacts (20 transmissions within 17 *Ec*-household clusters; Figure 3). A Spanish study revealed a lower rate of transmission among household members of 6 of 54 contacts (11.1%), but this may be explained by the different methodology of the studies [11]. Interestingly, in our study, there were 6 mother-to-child and 2 child-to-child pairs, which again suggest an important role for children in the ESBL epidemiology (Figure 3). With regard to the ESBL-*Ec*, the phylogenetic groups B2 (8 of 28 contacts) and D (9 of 34 contacts) tended to be more often transmitted within households

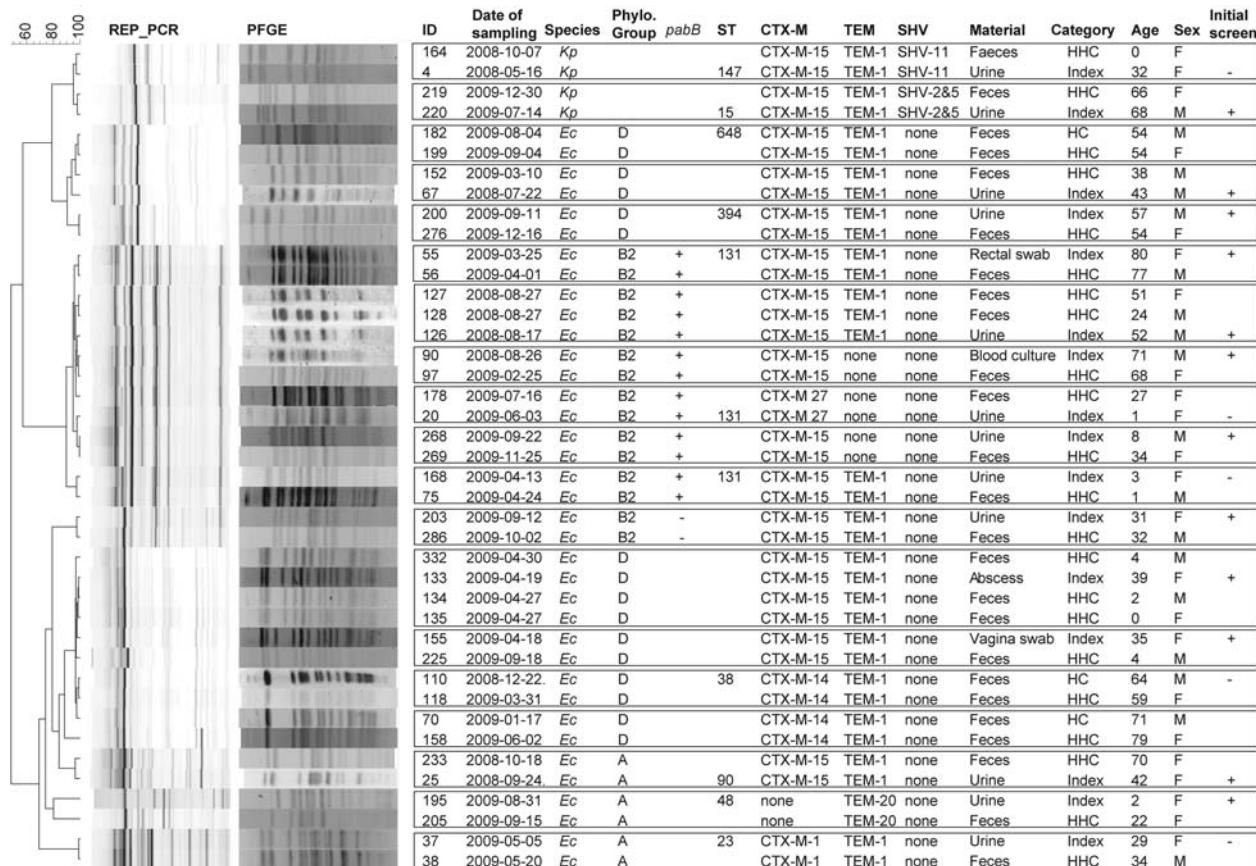
than groups A (3 of 19 contacts) and B1 (0 of 7 contacts), although this difference did not reach statistical significance ( $P = .1$ ). Nevertheless, the result is in accordance with groups B2 and D being more transmissible and virulent [21, 31].

Comparable with ESBL-*Ec*, the household transmission rate of ESBL-*Kp* was 25% (2 of 8 contacts). Because previous studies were limited to ESBL-*Kp* transmission in hospitals [32, 33], we are unable to compare our results with other studies, but we note that the ESBL-*Kp* STs involved in household transmission were of ST15 and ST147, which have been described elsewhere as epidemic [34].

Overall, for both ESBL-*Ec* and ESBL-*Kp* the net transmission rate was higher within the household than in the hospital, although this difference reached statistical significance only for ESBL-*Ec* ( $P < .001$ ). One of the explanations for this difference could be related to the longer exposure times in the outpatient household compared with the hospital setting.

### Detection Dynamics of ESBL Producers Not Linked to Transmission

A considerable number of ESBL producers detected by screening of hospital contact patients or household contacts could not be explained by transmission to an index patient (Supplementary Figure 1). In the hospital setting, this proportion was slightly higher than the prevalence of nosocomial transmissions for both ESBL-*Ec* (5.7% vs 4.5%) and ESBL-*Kp* (16.7% vs 8.3%). In particular, the dynamics of detection of ESBL producers in contact patients was quite similar for transmission and nontransmission events (Figure 4A). Probably, detection of ESBL producers requires some selection process (eg, exposure to antibiotics), which fluctuates during hospitalization. Thus, standard screenings (eg, selective agar plates) performed



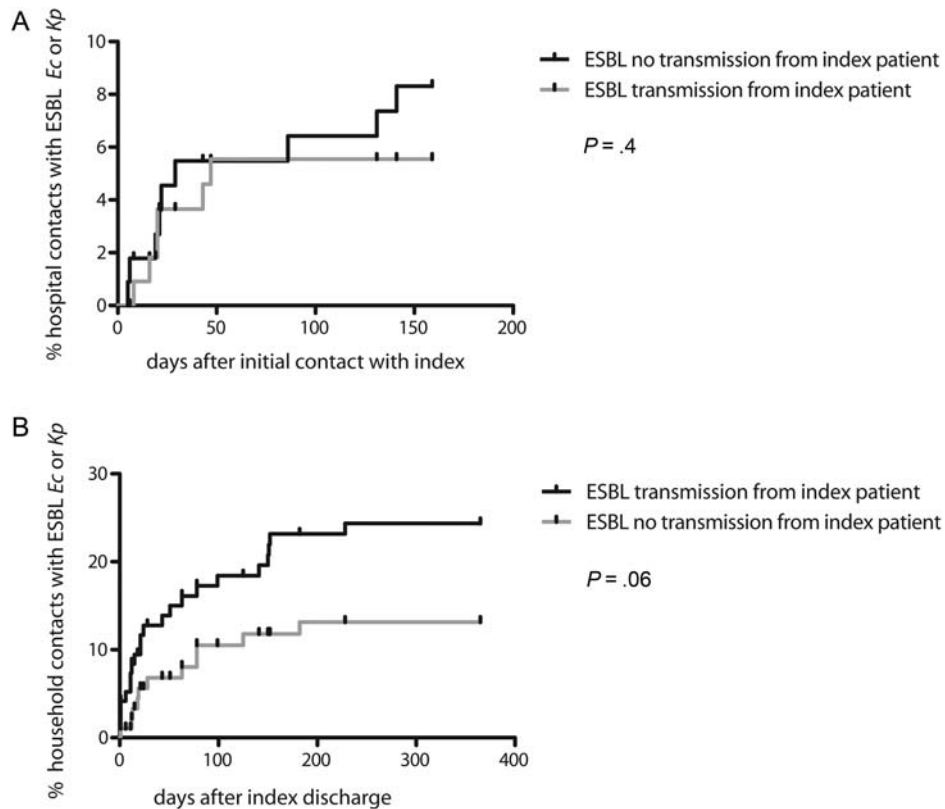
**Figure 3.** Characteristics of household transmissions of extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella pneumoniae*. Index patients, hospital contacts, and household contacts are indicated. Household clusters are shown in boxes. Presence of *pabB* gene is illustrated. Sequence types were determined according to Pasteur (*K. pneumoniae*) and Achtman (*E. coli*) multilocus sequence typing scheme. Abbreviations: *Ec*, *Escherichia coli*; HC, hospital contact; HHC, household contact; *Kp*, *Klebsiella pneumoniae*; PFGE, pulse-field gel electrophoresis; rep-PCR, extragenic palindromic polymerase chain reaction; ST, sequence type.

at one time point only (eg, at hospital entry) might therefore not identify all ESBL carriers. In the household setting, chance findings of ESBL carriage were less frequent than transmission events (ESBL-*Ec*, 12.5% vs 22.7%; ESBL-*Kp*, 0% vs 25%). However, the dynamics of ESBL detection over time were again quite similar for both groups (Figure 4B).

### Limitations of This Study

Our study has several limitations. First, the criteria for transmission in this study did not address the possibility of horizontal transmission of common plasmids among different Enterobacteriaceae species [35]. Thus, transmission rates might have been underestimated, but this hypothetical bias should have affected both household and hospital transmissions to the same extent. Second, our study could not address whether household transmission occurred from the index patients to other household members or by acquisition

from a common source. In fact, several studies have suggested that common sources such as food may contribute to the dissemination ESBL producers [12, 36]. However, for 2 household contacts (household contacts 118 and 158) person-to-person transmission was likely, because in both cases the corresponding patients (patients 110 and 70) acquired the ESBL producer during their hospital stay and transmitted it probably subsequently to their household contacts (Figure 3). In addition, the high prevalence of CTX-M-15-producing ESBL-*Ec* of ST131 also indicates person-to-person transmission because humans are the main reservoir of this clone [6, 37]. Overall, based on our data, we speculate that patients recently discharged from a hospital or cared for as outpatients may be a more efficient source of transmission in the community than healthy carriers. Whether such transmission can be controlled by preventative measures has to be evaluated.



**Figure 4.** Identification of extended-spectrum  $\beta$ -lactamase (ESBL) producers by Kaplan–Meier curves for the hospital contacts (A) and household contacts (B). “ESBL transmission” includes those contacts which were found to carry the same ESBL strain as the index patient, and “ESBL no transmission” describes contacts with ESBL carriage but without a match to the index patients’ strain (according to the definition given in the Methods). ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* are grouped together. Differences between the curves were calculated using the log-rank test. Abbreviations: *Ec*, *Escherichia coli*; ESBL, extended-spectrum  $\beta$ -lactamase; *Kp*, *Klebsiella pneumoniae*.

## Conclusions

To our knowledge, this is the first epidemiological study analyzing the transmission rates of ESBL producers in the household and the hospital setting simultaneously (ie, within the same period, within the same geographic area, and with the same index patients). Our data indicate that household transmission outweighs hospital transmission in a non-outbreak scenario and household transmission is enhanced in the presence of index patients recently discharged or cared for in a hospital. Furthermore, in the non-outbreak setting, importation of ESBL producers into the hospitals seems to be at least as frequent as transmission events during hospital stay. Our data also suggest that ESBL-*Kp* may be more efficiently transmitted within the hospital than ESBL-*Ec* and question the effect of infection control measures among different species. Further studies are needed to address the last issue.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>) Supplementary materials consist of data

provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

## Notes

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**Potential conflicts of interest.** All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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