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Original article

Household acquisition and transmission of extended-spectrum β-lactamase (ESBL) -producing *Enterobacteriaceae* after hospital discharge of ESBL-positive index patients

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ABSTRACT

Objectives: This study aimed to determine rates and risk factors of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE) acquisition and transmission within households after hospital discharge of an ESBL-PE-positive index patient.
Methods: Two-year prospective cohort study in five European cities. Patients colonized with ESBL-producing *Escherichia coli* (ESBL-Ec) or *Klebsiella pneumoniae* (ESBL-Kp), and their household contacts were followed up for 4 months after hospital discharge of the index case. At each follow up, participants provided a faecal sample and personal information. ESBL-PE whole-genome sequences were compared using pairwise single nucleotide polymorphism-based analysis.
Results: We enrolled 71 index patients carrying ESBL-Ec ($n = 45$), ESBL-Kp ($n = 20$) or both ($n = 6$), and 102 household contacts. The incidence of any ESBL-PE acquisition among household members initially free of ESBL-PE was 1.9/100 participant-weeks at risk. Nineteen clonally related household transmissions occurred (case to contact: 13; contact to case: 6), with an overall rate of 1.18 transmissions/100 participant-weeks at risk. Most of the acquisition and transmission events occurred within the first 2 months after discharge. The rate of ESBL-Kp household transmission (1.16/100 participant-weeks) was higher than of ESBL-Ec (0.93/100 participant-weeks), whereas more acquisitions were noted for ESBL-Ec (1.06/100 participant-weeks) compared with ESBL-Kp (0.65/100 participant-weeks). Providing assistance for urinary and faecal excretion to the index case by household members increased the risk of ESBL-PE transmission (adjusted prevalence ratio 4.3; 95% CI 1.3–14.1).

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Conclusions: ESBL-PE cases discharged from the hospital are an important source of ESBL-PE transmission within households. Most acquisition and transmission events occurred during the first 2 months after hospital discharge and were causally related to care activities at home, highlighting the importance of hygiene measures in community settings.
Clinical study registration: German Clinical Trials Register, DRKS-ID: DRKS00013250. **Maria E. Riccio, Clin Microbiol Infect 2021;27:1322**

Introduction

Transmission of extended-spectrum β-lactamase-producing *Enterobacteriaceae* (ESBL-PE) in the clinical setting has been extensively studied [1], but little is known about the risk and pathways of transmission in the community. A recent systematic review evaluating human-to-human ESBL-PE transmission between household contacts highlighted important limitations of previous studies [2]: low discriminatory power of previously applied typing methods for identifying ESBL-PE transmission events [3]; cross-sectional study design preventing the assessment of transmission dynamics over time; and no systematic assessment of ESBL-PE transmission paths and possible epidemiological determinants. Furthermore, only two studies focused on the likelihood of household transmission of ESBL-PE after hospital discharge of an ESBL-positive patient [4].

The aim of this study was to investigate ESBL-PE acquisition and transmission in household settings in five European cities with varying ESBL-PE baseline prevalence. Specifically, we attempted to determine the incidence and risk factors of ESBL-PE acquisition and transmission within families after hospital discharge of an ESBL-PE carrier.

Materials and methods

Study design

We conducted a prospective multicentre cohort study including ESBL-PE-positive patients and their household contacts from five university hospitals (Geneva, Sevilla, Tübingen, Utrecht, Besançon). The recruitment target was 20 households per centre (see Supplementary material, Appendix S1).

Population

Index cases were defined as intestinal ESBL-PE carriers discharged home into a household shared with at least one household contact. Household contacts were identified as any person sharing the same household with the index case at least three nights a week.

Inclusion and exclusion criteria

The inclusion criteria for the index cases were: to be $\geq$ 18 years old; to have a rectal swab or faecal sample at hospital discharge confirming intestinal colonization with ESBL-producing *Escherichia coli* (ESBL-Ec) and/or *Klebsiella pneumoniae* (ESBL-Kp); and to provide informed consent. Patients were excluded if they were permanently institutionalized or impossible to follow up. After inclusion, index cases were excluded if they had negative rectal samples during the first two visits. Enrolled participants who dropped out before collecting the first stool sample were also excluded.

Data collection

All participants were followed up for 4 months: at hospital discharge (baseline visit #1), 1 week (visit #2), 2 months (visit #3) and 4 months (visit #4). Questionnaires were filled out by all participants at visits #1, #2, #3, and #4. Collected variables concerned participants' health status, antibiotic intake, household conditions, dietary habits and lifestyle. All participants collected stool samples or rectal swabs themselves (or by a household contact) with Procult™ 500 kit (Ability Building Centre, Rochester, MN, USA) and faeces containers or Eswabs (Copan Diagnostics, Brescia, Italy) at visit #1, #2, #3 and #4 (±3 days). Collected information was transferred into a centralized REDCap database. The study was approved by each centre's institutional review board.

Microbiological methods

Selective culturing, enrichment broth, bacterial identification and antimicrobial susceptibility testing were performed for each stool sample or rectal swab at each centre's microbiology laboratory, using standardized methods (as described in the Supplementary material, Appendix S2).

Sequencing analysis

The full genome of ESBL-PE isolates was sequenced with NextSeq sequencer (Illumina, San Diego, CA, USA). DNA extraction was performed with DNeasy UltraClean Microbial Kit (Qiagen, Hilden, Germany). The sequence type (ST) of each isolate was identified by using seven housekeeping genes, using MLST version 2.10 (https://github.com/tseemann/mlst). ESBL-encoding genes were identified by Resfinder version 2.1 of the Center for Genomic Epidemiology [5]. Neighbour-joining core genome multi-locus sequence typing (cgMLST) trees were constructed with SeqSphere+ (Ridom, Münster, Germany) using the Enterobase scheme (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6961584/) for *E. coli* (2513 genes) and *sensu lato* scheme for *K. pneumoniae* (2358 genes). After removing genes not present in all strains, trees were built by comparing 1863 and 2088 genes, respectively. For strains presenting the same cgMLST alongside a strong epidemiological link, pairwise single nucleotide polymorphism (SNPs) distances were estimated using the CFSAN pipeline [6].

Definitions

Genomes of ESBL-PE isolates were considered clonally related and closely related when having, respectively, a pairwise distance of $\leq$10 or 11–25 SNP differences [7]. Acquisition was defined as newly identified carriage of an ESBL-Ec or ESBL-Kp strain during

follow up, not previously detected in the gut flora of the concerned participant. Transmission was defined as the newly detected intestinal carriage of ESBL-Ec and/or ESBL-Kp of a clonally related isolate previously identified in another household member. Co-carriage was defined as the simultaneous carriage by two or more household members of a clonally related isolate at the same sampling time-point.

Data analysis

Overall and species-specific incidence rates of acquisition and transmission were estimated at the genotypic level. Time at risk of ESBL-PE acquisition was estimated as the number of days between baseline and the acquisition of the corresponding pathogen in a participant previously free of it, or the drop out of the participant, or end of follow up, whichever occurred first. The time at risk of a possible ESBL-PE transmission was estimated as the time between baseline (for index cases) or the date of the first positive sample (for household contacts), and the first detection date of a clonally related isolate previously identified in another household member. Incidence rates were calculated as the total number of acquisition or transmission events divided by the total number of participant-weeks at risk multiplied by 100.

Risk factors of acquisition and transmission were evaluated by univariable and multivariable mixed-effects Poisson regression models to compute prevalence ratios [8,9], accounting for the lack of independence between repeated samples, and multiple clustering effects. The multilevel structure of the data was composed of three levels: participant (four samples per participant), household and study site. Potential confounders were chosen on the basis of existing evidence, and were only scored if exposure preceded the event, with final model selection performed using a stepwise backward model selection based on Akaike's information criterion [10]. Analyses were performed using R (version 3.6.3.) and STATA version 15 (StataCorp., College Station, TX, USA).

Results

Recruitment and household characteristics

Between November 2017 and April 2019, 71 households were included in the study, with 71 index cases and 102 of 127 eligible household contacts (participation rate, 80%). During the 4-month follow up, 35 participants from 14 households dropped out (Fig. 1). Important characteristics of participating households are shown in Table 1. The mean age of all participants was 53 ± 21 years; 47% were female.

Profile of index cases and household contacts

Baseline characteristics of index cases and household contacts are presented in Table 2 and in the Supplementary material (Table S1). During the hospital stay, 32% ($n = 23$) of index cases had an ESBL-PE infection and 39% ($n = 28$) received antibiotics at hospital discharge.

ESBL-PE carriage and acquisition

At baseline, index cases were carrying ESBL-Ec ($n = 45$, 63%) or ESBL-Kp ($n = 20$, 28%) or both ($n = 6$, 8%). Among household contacts already positive at baseline ($n = 29$, 31%), 79% (23/29) were carrying the same ESBL-PE as their corresponding index case. Twenty-six percent (17/65) of household contacts with complete follow up acquired ESBL-PE (ESBL-Ec, 11; ESBL-Kp, 6). Most ESBL-PE acquisitions occurred during the first 2 months (1st week: 41%; 2nd to 8th week: 29%). One-third of index cases ($n = 27$) were ESBL-PE negative at the end of follow up.

Genetic profiles

Overall, 38 different STs were observed for ESBL-Ec and 29 for ESBL-Kp (see Supplementary material, Fig. S1). Among ESBL-Ec strains, ST131 was the most frequent ST (46%). Less frequent STs were ST38 (6.9%), ST1193 (4%) and ST10 (3.6%). STs from ESBL-Kp showed a large heterogeneity (see Supplementary material, Fig. S2). Of 44 different ESBL-encoding genes identified, the most frequent was $bla_{\text{CTX-M-15}}$, detected in 142 ESBL-Ec and 79 ESBL-Kp isolates.

Clonally related co-carriage and transmission of related isolates

At baseline, 14 out of 29 positive household contacts had isolates clonally related to the index case. The overall prevalence of co-carriage of clonally related isolates was 34% (32/94) over the entire study period.

By combining epidemiological information with whole-genome sequencing data (Fig. 2), 19 clonally related transmission events were identified showing two possible directions: from the index case to his/her household contacts ($n = 13$) and vice versa ($n = 6$). Two additional closely related transmission events were identified for household BE07 from Besançon (18 to 24 SNP differences). The isolates belonged to ST80 and the intra-individual genome variability of the ESBL-Ec isolates retrieved from the index case throughout all sampling points ranged from 7 to 11 SNP differences. Most of the transmissions involved ESBL-Ec (14/21), with nine of them transmitted by the index case (Table 3 and see Supplementary material, Table S2). Fifteen of 21 (71%) transmission events occurred during the first 2 months of follow up. The phylogenetic trees of retrieved ESBL-Ec and ESBL-Kp strains are shown in the Supplementary material (Figs S3 and S4).

Incidence rates of household acquisition and transmission of ESBL-PE

The overall ESBL-PE acquisition rate was 1.9/100 participant-weeks at risk (Table 3). ESBL-Ec had a higher rate of acquisition than ESBL-Kp (1.06 versus 0.65/100 participant-weeks at risk; relative risk (RR) 1.65; 95% CI 0.69–3.95). The rate of any clonally related ESBL-PE transmission within households was 1.18 events/100 participant-weeks of follow up, with the corresponding figure for transmissions only from the index case to household contacts of 0.8/100 participant-weeks (Table 3). Although not statistically significant, a higher overall transmission rate was observed for ESBL-Kp than for ESBL-Ec (1.16 versus 0.93 per 100 participant-weeks at risk; RR 1.25; 95% CI 0.42–3.44) considering all possible transmission paths. A higher rate of ESBL-Kp transmission was also observed from index cases to household contacts (RR 1.87; 95% CI 0.52–6.49).

Risk factors for ESBL-PE acquisition and transmission

By univariable, mixed-effects Poisson regression, multiple explanatory factors were significantly associated with the risk of acquiring ESBL-PE among previously ESBL-PE-free household contacts (see Supplementary material, Table S3): (a) index case determinants: hemiplegia, faecal incontinence, previous abdominal infection, proton-pump inhibitor therapy, three or more antibiotic courses after discharge, additional hospitalizations, and assistance provided by household members, in particular for urinary and faecal excretion; (b) household member determinants:

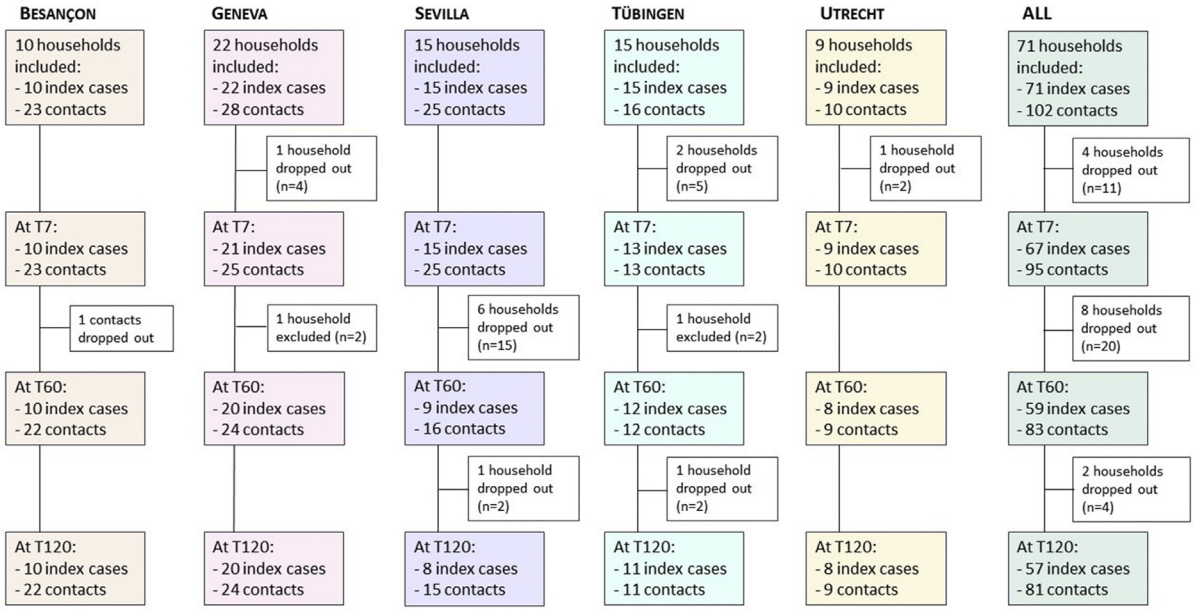

Fig. 1. Study flow diagram of study participants, by centre and overall.

Table 1
Characteristics of households included in the study

	ESBL-Ec	ESBL-Kp	ESBL-Ec and ESBL-Kp
	n (%)	*n* (%)	*n* (%)
Total *n*	45	20	6
Study site			
Besançon	7 (15.6)	3 (15.0)	0
Geneva	12 (26.7)	6 (30.0)	4 (66.7)
Sevilla	9 (20.0)	6 (30.0)	0
Tübingen	11 (24.4)	2 (10.0)	2 (33.3)
Utrecht	6 (13.3)	3 (15.0)	0
Number of participating household members			
2	33 (73.3)	14 (70.0)	5 (83.3)
3	7 (15.6)	3 (15.0)	1 (16.7)
>4	5 (11.1)	3 (15.0)	0
Children in the household			
<18 years	9 (20.0)	7 (35.0)	1 (16.7)
<5 years	3 (6.7)	4 (20)	0
Household exposure to at least two antibiotics during follow up			
T60	7 (15.6)	3 (15.0)	0 (0)
T120	7 (15.6)	1 (5.0)	0 (0)
Number of toilets in household			
>2	17 (39.5)	8 (40.0)	3 (60.0)
Bath separated from toilet	16 (36.4)	3 (15.0)	2 (33.3)
Surface area of living space (m^2), median ± SD	122.2 ± 69.7	154.2 ± 82.3	132 ± 45.7
Vegetarians in household	1 (2.3)	1 (5.0)	0

Abbreviations: ESBL, extended-spectrum β-lactamase; ESBL-Ec, ESBL-producing *Escherichia coli*; ESBL-Kp, ESBL-producing *Klebsiella pneumoniae*; ESBL-PE, ESBL-producing *Enterobacteriaceae*.
Data are reported as *n* (%), unless stated otherwise.

age >50 years, travel abroad, assistance provided by healthcare personnel, help requested for various activities, regular contact with domestic animals, meat and seafood exposure, as well as the number of antibiotic courses. By multivariable analysis in a parsimonious model, assistance provided by family members to the index case (adjusted prevalence ratio (aPR) 2.9; 95% CI 1.1–8.0) showed the strongest association with ESBL-PE household acquisition, whereas frequency of meat consumption (aPR 1.4; 95% CI 0.4–5.3) and antibiotic exposure (aPR 1.4; 95% CI 0.4–4.2) showed only weak evidence of a positive association.

Fourteen variables were found to be significantly associated with the risk of ESBL-PE transmission from the index case to household members in the univariable analysis (see Supplementary material, Table S4): (a) index case determinants: higher education (protective), full autonomy (protective), malignancy, faecal incontinence, previous abdominal infection, urinary catheter, proton-pump inhibitor therapy, three or more antibiotic courses, two or more hospitalizations, and assistance provided by family members, in particular for urinary and faecal excretion; (b) household member determinants: spouse of index case, antibiotic intake and active helper of index case. In the final multilevel Poisson regression model, assistance provided by household members for urinary and faecal excretion was strongly associated with increased risk of ESBL-PE transmission (aPR 4.3; 95% CI 1.3–14.1),

Table 2
Main characteristics of ESBL-PE-positive index cases included in the study

	ESBL-Ec ($n = 45$)	ESBL-Kp ($n = 20$)	ESBL-Ec and ESBL-Kp ($n = 6$)
Demographic			
Age (years), median (range)	62 (21–89)	64 (28–96)	57.5 (51–83)
Female gender	16 (35.6)	9 (45.0)	2 (33.3)
Highest education			
Primary school	11 (24.4)	7 (35.0)	0
Secondary school	11 (24.4)	8 (40.0)	0
Technical school	11 (24.4)	4 (20.0)	0
University	5 (11.1)	1 (5.0)	5 (83.3)
Other/unknown	7 (15.6)	0	1 (16.6)
Antibiotic exposure in previous 12 months	19 (42.2)	8 (40.0)	1 (16.7)
Travel abroad in previous last 12 months	23 (52.3)	5 (25.0)	4 (66.7)
Dietary habits			
Omnivore	42 (97.7)	19 (95)	5 (83.3)
Weekly meat consumption	38.5 (86.0)	20 (100)	4 (67)
Vegetarian	1 (2.3)	1 (5.0)	0
Hospital length of stay			
1–7 days	19 (42.2)	3 (15.0)	3 (50.0)
8–14 days	10 (22.2)	6 (30.0)	1 (16.7)
15–28 days	8 (17.8)	6 (30.0)	0
>28 days	8 (17.8)	5 (25.0)	2 (33.3)
Co-morbidities	40 (88.9)	18 (90.0)	5 (83.3)
Autoimmune disease	0	2 (10.0)	0
Cardiovascular disease	20 (44.4)	7 (35.0)	2 (33.3)
Chronic dermatological disease	4 (8.9)	1 (5.0)	1 (16.7)
Chronic renal failure	7 (15.6)	1 (5.0)	0
Chronic obstructive pulmonary disease	3 (6.7)	2 (10)	0
Diabetes	14 (31.1)	3 (15.0)	0
Gastrointestinal disease	7 (15.6)	3 (15.0)	0
Chronic diarrhoea	1 (2.2)	0	0
Hepatic disease	4 (8.9)	2 (10.0)	0
Inflammatory bowel disease	3 (6.7)	2 (10)	0
Hemiplegia	0	1 (5.0)	0
Immunosuppression	5 (11.1)	4 (20.0)	1 (16.7)
Malignancy	14 (31.1)	9 (45.0)	1 (16.7)
Other	19 (42.2)	10 (50.0)	4 (66.7)
ESBL-PE infection during hospitalization			
Yes	15 (33.3)	5 (25.0)	3 (50.0)
No	26 (57.8)	13 (65.0)	3 (50.0)
Unknown	4 (8.9)	2 (10.0)	0
Antibiotics at discharge			
Yes	19 (42.2)	8 (40.0)	1 (16.7)
No	26 (57.8)	11 (55.0)	4 (66.7)
Unknown	0	1 (5.0)	1 (16.7)
Incontinence	6 (13.3)	6 (30.0)	0
Urinary incontinence	3 (6.7)	4 (20.0)	0
Faecal incontinence	2 (4.4)	2 (10.0)	0
Both	1 (2.2)	0	0
Indwelling device at discharge	34 (75.6)	12 (60.0)	5 (83.3)
Intravascular	4 (8.9)	4 (20.0)	1 (16.7)
Urinary	1 (2.2)	2 (10.0)	0
Other	7 (15.6)	2 (10.0)	0
Patient autonomy			
Not completely autonomous	19 (42.2)	11 (55.0)	3 (50.0)
Needs support by family members	12 (26.7)	8 (40.0)	2 (33.3)
Help required for urinary or faecal excretion	2 (4.4)	6 (30.0)	0
Home care by healthcare personnel	12 (26.7)	5 (25.0)	1 (16.7)

Abbreviations: ESBL, extended-spectrum β-lactamase; ESBL-Ec, ESBL-producing *Escherichia coli*; ESBL-Kp, ESBL-producing *Klebsiella pneumoniae*; ESBL-PE, ESBL-producing *Enterobacteriaceae*.
Data are reported as *n* (%), unless stated otherwise.

whereas household antibiotic exposure showed weaker evidence of a positive association (aPR 2.1; 95% CI 0.7–7.0).

Discussion

The principal findings of this international cohort study were: (a) clonally related ESBL-PE household transmission after hospital discharge of an ESBL-PE carrier occurred in 19 of 94 participants; (b) most acquisition and transmission events were observed during the first 2 months; (c) other household members were potential sources of cross-transmission, but to a lesser degree; (d) the ESBL-PE acquisition rate was higher than the transmission rate; so, exogenous acquisition events occurred even without intra-household transmission; (e) the rate of household transmission was higher for ESBL-Kp than for ESBL-Ec; and (f) assistance provided by family members for urinary and faecal excretion of the index case was the most important risk factor for ESBL-PE transmission.

A recent meta-analysis examining clonally related ESBL-PE among household members documented co-carriage proportions of 12% (95% CI 8%–16%), and acquisition rates ranging from 0.16 to 0.20 events/100 participant-weeks of follow up [2]. In contrast, our

Fig. 2. Transmission events of clonally related and closely related isolates of extended-spectrum β-lactamase (ESBL) -producing *Escherichia coli* and *Klebsiella pneumoniae*, with direction of the transmission pathways. The figure gives the sequence type of the transmitted strains and pairwise single nucleotide polymorphism (SNP) differences between the isolates concerned. Each line of the table contains the information for a single household. Each square box represents a sample from a participant at a given sampling time-point (i.e. #1, #2, #3, #4). Red and green colours correspond to samples positive with ESBL-producing *E. coli* and *K. pneumoniae*, respectively. Grey colour corresponds to samples that were negative for ESBL-producing *Enterobacteriaceae*. Transmission events were identified in two directions: from index case (A) to household members (B to E) and from household contacts to index case. Red boxes (with *) represent clonally related ESBL-producing *E. coli* strains and green boxes (with *) represent clonally related ESBL-producing *K. pneumoniae*. MLST, multilocus sequence type.

Table 3
Crude numbers and incidence rates of acquisition and transmission events, based on core genome multi-locus sequence typing with pairwise single nucleotide polymorphism differences

	Acquisitions from any source			Transmissions in any direction			Transmissions from index case to household contacts		
	ESBL-Ec	ESBL-Kp	ESBL-PE	ESBL-Ec	ESBL-Kp	ESBL-PE	ESBL-Ec	ESBL-Kp	ESBL-PE
Crude number	13	12	17	12	7	19	7	6	13
Incidence rate (per 100 participant-weeks at risk)	1.06	0.65	1.90	0.93	1.16	1.18	0.53	1.00	0.80

Abbreviations: ESBL, extended-spectrum β-lactamase; ESBL-Ec, ESBL-producing *Escherichia coli*; ESBL-Kp, ESBL-producing *Klebsiella pneumoniae*; ESBL-PE, ESBL-producing *Enterobacteriaceae*.

study observed higher co-carriage proportions (34%) and 10-fold higher acquisition rates (1.9 events per 100 participant-weeks at risk). The higher proportion of co-carriage in the present study might have been influenced by sampling and detection methods, as the use of enrichment broths and selection of multiple colonies per sample might have improved the yield. Furthermore, it may reflect a higher risk of ESBL-PE transmission within enrolled households before study participation. The differences in acquisition rates depend on the length of follow up: longer follow up periods result in smaller rates. Indeed, 12-month follow-up studies found lower acquisition rates in contrast to shorter follow-up studies, which reported acquisition rates of up to 1.74 closely related ESBL-PE/100 person-weeks [2,8,11]. Furthermore, the higher proportion of infected, dependent and antibiotic-treated index cases in our study might have increased early transmission risk for household members compared with previous studies.

The incidence of ESBL-Ec acquisition was higher than the rate for ESBL-Kp. In contrast, household transmission rates were higher for ESBL-Kp compared with ESBL-Ec. This apparent contradiction is explained by the acquisition of ESBL-Ec from a wide range of sources (e.g. food, animals, travel) [12,13], whereas transmission, as defined here, only involved human-to-human transfer. Similar observations have also been described for healthcare settings, suggesting that biological differences between bacterial species could explain higher ESBL-Kp transmission rates [14,15]. An alternative explanation might be the slightly higher intra-species diversity of ESBL-Ec within households (mean number of different STs observed per family 1.6 in ESBL-Ec versus 1.3 in ESBL-Kp). Furthermore, the frequency and intensity of human interactions may facilitate transmission of ESBL-KP, especially among elderly patients [16]. Indeed, in our study, index patients carrying ESBL-Kp were sicker and more dependent on external care, leading to increased proximity and risk of transmission.

As *Enterobacteriaceae* are colonizers of the intestinal tract, the faecal–oral route plays an important role in the transmission chain. As in healthcare settings, where hand hygiene has been shown to be a key factor to reduce pathogen transmission [17], general hygiene measures rather than decreased intake or inappropriate handling of contaminated food may become an important preventive measure to reduce ESBL-PE transmission within

households, especially if family members provide assistance to a sick relative [18].

Hitherto, no previous study with these design characteristics and high-resolution typing methods has been conducted in high-income settings to ascertain putative transmission events within entire families, although ESBL-PE acquisition and transmission in the community or low-income settings has previously been investigated [11,12,19–24]. Therefore, the present study provides a solid methodological foundation for future studies and prioritization of infection control interventions in the community setting.

Several limitations of this study merit consideration. First, not all members living in the same household participated in the study, omitting possible transmission events. Fortunately, the participation rate was high enough (80%) to draw meaningful conclusions. Second, by choosing not more than four colonies from a faecal sample, clonally distinct strains might have been missed, introducing a possible selection bias and underestimating the true transmission rate. As observed in a few participants (16%), each host may carry several ESBL-Ec strains simultaneously. However, we hypothesize that isolates not retrieved might present a low inoculum with lower transmission risk compared with dominating ESBL-Ec strains. Third, we did not yet conduct plasmid typing, which is part of a complementary investigation, providing a more comprehensive picture of ESBL transmission in the community, especially for *E. coli*. Fourth, the role of intermediate vectors (i.e. animal) or environmental reservoirs (i.e. surfaces, water) in ESBL-PE transmission was not directly examined, but was assumed as part of direct human-to-human transmission. However, fomite-mediated transmission was accounted for in the estimation of exogenous risk factors by collecting relevant epidemiological information. Fifth, participants' intestinal load of ESBL-PE was not quantified, preventing the consideration of the inoculum effect as an independent risk factor. However, the bacterial load is influenced by several factors that were collected and accounted for in the analysis (e.g. antibiotic exposure, hospital length of stay).

In summary, ESBL-PE carriers discharged from the hospital were an important source of ESBL-PE transmission within households. Most acquisition and transmission events occurred during the first 2 months after hospital discharge. They were associated with care activities at home, highlighting the importance of hygiene measures to prevent community spread.

Previous presentations

Preliminary results of this study were presented online at the 30th European Congress of Clinical Microbiology and Infectious Diseases in Paris, France in April 2020 (abstract #6380). Preliminary results of this study were also presented at the 5th International Conference on Prevention & Infection Control, in Geneva, Switzerland, in September 2019 (abstract #O35).

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Transparency declaration

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. SH reports personal fees from Sandoz, outside the submitted work. SP reports advisory board and speaker honoraria from Biomérieux, Illumina and IDbyDNA outside the submitted work. All other authors have nothing to disclose.

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Author contributions

All co-authors contributed to the study design or conduct. SH, ET, MEAK, JRB, MER and RM wrote the study protocol. SH, JRB, JAJWK, ET, DH and BSC obtained funding. MER, ES, TV, DM, AM and NC contributed to recruitment and enrolment of participants in their local institution. AC, ACF, SP, JG, MD, DM, AM and DH performed or supervised the microbiological analyses in their local centres. JAJWK, ACF, SP and JG provided a standardized procedure for whole-genome sequencing. JAJWK and ACF supervised sequencing. MER, RM, JS, MEAK, BC and SH performed or contributed with their expertise to statistical analyses. MER, TV and JP performed genetic analyses. SH, JRB, JAJWK, ET and DH supervised the study in their local institution as principal investigators. SH and MER coordinated activities among the centres. MER, RM and SH drafted the manuscript and all authors reviewed and contributed to the manuscript. SH coordinated the project.

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Appendix A. Supplementary data

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