Clinical Microbiology and Infection 23 (2017) 46.e1–46.e7

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Quantifying within-household transmission of extended-spectrum β-lactamase-producing bacteria

M.R. Haverkate [1,*,9], T.N. Platteel [2,3,9], A.C. Fluit [2], J.W. Cohen Stuart [4], M.A. Leverstein-van Hall [5,6], S.F.T. Thijsen [7], J. Scharringa [2], R.C. Kloosterman [2], M.J.M. Bonten [1,2], M.C.J. Bootsma [1,8]

[1] Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands
[2] Department of Medical Microbiology, University Medical Centre Utrecht, Utrecht, The Netherlands
[3] SALTRO, Department of Medical Microbiology, Utrecht, The Netherlands
[4] Department of Medical Microbiology, Medisch Centrum Alkmaar, Alkmaar, The Netherlands
[5] Department of Medical Microbiology, Bronovo Hospital, den Haag, The Netherlands
[6] Department of Medical Microbiology, Alrijne Hospital, Leiden, The Netherlands
[7] Department of Medical Microbiology, Diakonessenhuis, Utrecht, The Netherlands
[8] Department of Mathematics, Utrecht University, Utrecht, The Netherlands

A R T I C L E I N F O

Article history:
Received 14 May 2016
Received in revised form
24 July 2016
Accepted 13 August 2016
Available online 3 September 2016

Editor: M. Paul

Keywords:
Extended-spectrum beta-lactamase (ESBL)
Within-household transmission
Enterobacteriaceae
Mathematical model
Colonisation

A B S T R A C T

Objectives: Patients can acquire extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* during hospitalization, and colonized patients may transmit these bacteria after discharge, most likely to household contacts. In this study, ESBL transmission was quantified in households.
Methods: Faecal samples were longitudinally collected from hospitalized patients colonized with ESBL-producing bacteria and from their household members during hospitalization of the index patient and at 3, 6, 12 and 18 months. A mathematical household model was developed, which allowed for person-to-person transmission, acquisition from other sources (background transmission), and losing carriage. Next, a deterministic population model with a household structure was created, informed by parameter values found in the household model.
Results: In all, 74 index patients and 84 household members were included. In more than half of the household members ESBL-producing bacteria were demonstrated at some time during follow up. Person-to-person transmission occurred at a rate of 0.0053/colonized person/day (0.0025–0.011), background transmission at 0.00015/day (95% CI 0.00002–0.00039), and decolonization at 0.0026/day (0.0016–0.0040) for index patients and 0.0090/day (0.0046–0.018) for household members. The estimated probability of transmission from an index patient to a household contact was 67% and 37% vice versa.
Conclusion: There is frequent transmission of ESBL-producing bacteria in households, which may contribute to the observed endemicity of ESBL carriage in the Netherlands. However, the population model suggests that there is not a single dominant acquisition route in the community. **M.R. Haverkate, CMI 2017;23:46.e1–46.e7**
© 2016 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

Introduction

In recent years, the worldwide prevalence of extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* has increased [1–5]. Resistance rates are especially high in healthcare settings, most likely because of cross-transmission and antibiotic selective pressure. Community-acquired infections with ESBL-producing bacteria are also on the rise and there is evidence for community spread of ESBL-producing *Escherichia coli* [1,3]. Urinary

* Corresponding author. M. Haverkate, Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Huispost Geuns 5.02, Heidelberglaan 100, 3584 CK Utrecht, The Netherlands.
E-mail address: m.r.haverkate-2@umcutrecht.nl (M.R. Haverkate).
[9] The authors M.R. Haverkate and T.N. Platteel contributed equally to this work.

http://dx.doi.org/10.1016/j.cmi.2016.08.021
1198-743X/© 2016 European Society of Clinical Microbiology and Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

tract infections constitute the major part of these infections. In the Netherlands, one in ten patients visiting their general practitioner with gastrointestinal complaints appeared to be colonized with ESBL-producing bacteria [6].

The underlying mechanisms of the established ESBL endemicity in the community are not well understood. After hospital discharge, colonized patients can transmit contracted bacteria to others in the community, especially within the household setting where people have close contacts. Reported colonization prevalence in household contacts of ESBL carriers has ranged from 17% to 32% [7–12]. Although within-household transmission of ESBL-producing bacteria was assessed in several studies [7,10,13,14], transmission rates have never been determined.

The duration of carriage represents the duration of infectiousness and of increased risk for an infection with ESBL-producing bacteria. Estimates for the duration of carriage of ESBL-producing bacteria vary, but they can persist for more than a year [12,15–18]. Furthermore, travellers returning from areas with high prevalence of ESBL-producing bacteria introduce these bacteria into the community [19,20], and several studies have suggested that transmission of ESBL-producing bacteria may occur through the food chain [21–23].

The aim of our study was to determine the transmission capacity of, and duration of colonization with, ESBL-producing bacteria in households with previously hospitalized patients. We included the calculated parameters in a population model to quantify the contributions of nosocomial, within-household, and travel-associated acquisitions to the community prevalence of ESBL.

Materials and methods

Study population and data collection

Data were collected from all patients with a newly recognized infection or colonization with bacteria suspected of ESBL-production (lowered susceptibility for cefotaxime or ceftazidime, confirmed by Etest) admitted between July 2010 and October 2013 to the University Medical Centre Utrecht, the Diakonessenhuis, or Wilhelmina Children's Hospital in Utrecht, the Netherlands. Patients needed to have an expected survival of at least 1 year. They will be referred to as index patients. They were included based upon clinical culture results, which could be obtained from any body site and on clinical indication or for screening purposes. The first clinical culture suspected of ESBL-production per patient was included.

After patient inclusion, a faecal sample was obtained during hospitalization. Furthermore, all household contacts of index patients, defined as persons who shared the same household with the index patient on a regular basis, were asked to participate. Faecal samples and questionnaires were collected during the hospital stay of the index patient, which will be referred to as T0.

After discharge, index patients and household contacts were followed up with faecal samples and questionnaires at 3 (T3), 6 (T6), 12 (T12), and 18 (T18) months. Follow up was also continued when cultures were negative for ESBL. Follow up was discontinued for household contacts if the index patient was lost to follow up. Information on antibiotic use was derived from both pharmacy departments and community-based pharmacies. If the day of sample collection was not exactly the same for all household contacts, the mean day was used in the analyses.

Informed consent was obtained from all participants. This study was approved by the medical ethical committee of the University Medical Centre Utrecht.

Microbiology

All cultures were inoculated on an ESBL Brilliance plate (Thermo Fisher Scientific, Paisley, UK) to detect ESBL-producing strains and on MacConkey agar (Thermo Fisher Scientific, Paisley, UK) as a control for adequate sampling. Growth on MacConkey agar, but not on ESBL Brilliance plates, was defined as ESBL-negative; growth on ESBL Brilliance plates was defined as possible ESBL carriage. Isolates obtained from ESBL Brilliance plates were investigated by microarray analysis (Check-Points, Wageningen, the Netherlands) for the presence of ESBL genes. PCR, DNA sequencing, and species identification using matrix-assisted laser desorption/ionization time-of flight mass spectrometry (Bruker Daltonik, Bremen, Germany) were performed on ESBL-positive isolates. All morphologically different colonies were tested for the presence of ESBL genes. Participants were informed about their ESBL carriage status.

Relatedness of isolates was determined at the level of the bacterial strain, ESBL gene and plasmid. This was assessed for families consisting of at least two persons, of which the index patient had an ESBL-positive clinical culture or T0 screening culture and at least one household member had a positive follow-up culture. Relatedness was determined for the first isolated culture of the household contact with the same ESBL gene as identified from the index patient and the previous ESBL-positive culture of the index patient. Strain relatedness was also investigated using an isolate obtained during hospitalization and the last follow-up isolate with a similar ESBL gene.

The ESBLs were considered related if the ESBL gene and plasmid incompatibility group were the same, according to PCR, sequencing and PCR-based replicon typing (PBRT). Strain relatedness was based on DiversiLab typing (BioMérieux, Marcy l'Etoile, France). Occurrence of ESBL relatedness in the absence of strain relatedness was considered as occurrence of within-host plasmid transfer. Isolates with similarities of >98% in DiversiLab typing were considered similar. Isolates with similarities of <98% were judged manually using the pattern overlay of the analysis tool in the software [24].

From sets of isolates (the first and last isolate available) from the same patient with similarities of <98%, plasmids were typed with PBRT after transformation, as previously described [25]. For sets of isolates with similarities of >98%, PBRT was performed without transformation. If plasmid types were not similar, PBRT and DiversiLab were also performed for all other ESBL-producing isolates of that patient.

Household model

To estimate transmission rates and decolonization rates we developed a Markov model, taking false-negative results, missing results and unobserved colonization times into account. All 74 index patients and 84 household members were included in the model. A detailed description including a visualization of the model in a figure can be found in the Supplementary material (Information S1).

Participants could be in one of two states: colonized or uncolonized with ESBL-producing bacteria. Patients were assumed to have a probability f to acquire ESBL-producing bacteria during hospital stay. Household contacts of the patients had a probability g to be colonized when their family member was hospitalized. ESBL-positive participants could lose colonization with rate γ. Person-to-person transmission was captured in β. As transmission and decolonization rates might be different for index patients and household members, for example because of functional status, we estimated γ_1 and β_1 for index patients and γ_2 and β_2 for household members, respectively. Transmission rates were also determined for subjects below the age of 5 years and all other ages. A constant background transmission rate α was assumed to account for

transmission from other sources. Assuming 100% specificity, the sensitivity ϕ was estimated, accounting for the fact that negative cultures could be false negative. Time was measured in days.

We assumed that participants had a fixed number of contacts per day with their household members (or with objects contaminated by positive household members) and if more household members were present, this fixed number should be 'divided' over all household members (frequency-dependent transmission). In the Supplementary material (Information S2) the results under the assumption of density-dependent transmission are shown, where the number of contacts per day increases with the household size.

A maximum likelihood method was used to simultaneously estimate the model parameters. We assumed that transmission could only take place after the first culture taken in the hospital. Transmission from an index patient to a household member and back was allowed in the model. The probability of transmitting ESBL-producing bacteria during the infectious period to a household contact was calculated as $\beta_i/(\beta_i+\gamma_i)$ for both index patients and household members. The different model variants are presented in the Supplementary material (Information S3). Model fit was evaluated using the likelihood ratio test. Calculations were performed in Mathematica 9.0 (Wolfram Research, Inc., Mathematica, Version 9.0, Champaign, IL, USA).

Population model

In order to study the effect of household transmission on the population level, a deterministic population model was constructed consisting of households of size one to five. Information on the household size distribution in the Netherlands was obtained from the Dutch Bureau of Statistics (CBS). Using a maximum household size of five persons ensures that more than 95% of the Dutch population was covered [26]. Parameters as estimated in the transmission model were used to inform the population model. In the population model, ESBL-negative persons could acquire ESBLs during hospital stay (α_1), during travel to a region with a high prevalence of ESBL (α_2), and due to transmission originating from an ESBL-positive person (β). Homogeneous mixing was assumed both at the level of contacts within the households and at the level of between-household contacts [27]. The transmission parameter β and decolonization rates γ_1 and γ_2 found in the transmission model were used in the population model.

In the first analysis, we only allowed for within-household transmission, to explore the effects of this parameter on the population-wide prevalence. Subsequently, we added the possibility of between-household transmission and an unknown parameter representing all other possibilities of exogenous acquisition (such as consumption of contaminated food or transmission from companion animals).

Results

Baseline characteristics

In total, 74 index patients and 84 household contacts were included in the study. Household sizes ranged from one to five persons, with 20 single households, 39 couples, three families of three, nine families of four, and three families of five. For computational reasons, one family of ten (with only complete data at T0) was excluded.

Mean age at enrolment was 54 years for index patients and 43 years for household contacts. Half (51%) of the included household contacts were partner of the index patient, 23% were a parent, 13% a child, and 13% a sibling. Fifty-one per cent of the index patients and 46% of the household contacts were male (Table 1). After 3 months, 12% of families were lost to follow up, at 6 months 19%, at 12 months 35%, and at 18 months 48%. Hospitalization was common for the index patients, but not the household members: between T0 and T3 55% of the index patients and 0% of the household members were hospitalized, between T3 and T6 38% and 0%, between T6 and T12 44% and 2%, and between T12 and T18 31% and 2%, respectively. Antibiotic use was common for index patients, but rare for household members (see Supplementary material, Information S4). The functional status of the index patients was not documented, but at every time-point at most four index patients were not residing at home (but in a nursing home or rehabilitation centre). In the year before enrolment, 36 index patients (49%) travelled outside of the Netherlands, with 11 (15%) outside Europe. For household members, this was 45 (54%) and ten (12%), respectively.

Relatedness of ESBLs

As mentioned, relatedness was assessed for families consisting of at least two persons, of which the index patient had an ESBL-positive clinical culture or T0 screening culture and at least one household member had a positive follow-up culture. Isolates of 32 index patients and 53 household contacts were selected (Table 2). In 31 of 53 (58%) household contacts ESBL-producing bacteria were demonstrated at some time during follow up; in 19 of 26 (73%) partners, six of 11 (55%) parents, five of nine (56%) children and one of seven (14%) siblings. Acquisitions of related ESBLs between sample moments were observed, as well as loss of colonization.

In 13 of the 16 (81%) household contacts colonized with ESBL-producing bacteria at T0, ESBLs were related to those of the index patient. These 13 household contacts originated from 11 households. In six of the 11 index patients belonging to these 11 households, their first culture was obtained within 3 days after hospital admission and was producing ESBLs. In these patients it was, therefore, not excluded that they were already colonized at hospital admission. Cultures obtained within 3 days after hospital admission were not available for the other five index patients.

Of strains with related ESBLs, 12 were clonally related *E. coli* isolates and the other strain was an unrelated *Klebsiella pneumoniae* isolate. Nine household contacts were partners, three parents and one a sibling of the index patient.

Household model estimates

All 74 index patients and 84 household members were included in the model. In the best fitting model, 52% of the included patients (95% CI 41–61) were positive based on the first in-hospital screening culture, as were 24% (95% CI 16–35) of the household members at that time (T0).

The person-to-person transmission (β) and background transmission rates (α) were estimated to be 0.0053 (95% CI 0.0025–0.011) per colonized person per day and 0.00015 (95% CI 0.00002–0.00039) per day, respectively. No significant difference was found between the transmission rate from an index patient and from a household member or from children below the age of 5 years. The sensitivity of the faecal screening (ϕ) was estimated to be 74% (95% CI 64–84). Estimated decolonization rates were 0.0026 (95% CI 0.0016–0.0040) and 0.0090 (95% CI 0.0046–0.018) for index patients and household members, respectively, reflecting a longer median duration of colonization for index patients compared with household members (267 days; 95% CI 173–433 versus 111 days; 95% CI 56–217). A model with different susceptibilities for acquisition for index patients and household members did not perform significantly better (data not shown).

Table 1
Baseline characteristics

		Index patients ($n = 74$), n (%)	Household contacts ($n = 83$)[a], n (%)
Gender (male)		38 (51.4)	38 (45.8)
Age, years, mean [SD]		54 [24]	43 [23]
Household contacts, median [IQR]		1 [0–1]	
Days between hospital admission and first screening culture, median [IQR]		19 [11–35]	
Hospital admission in 3 months before current admission		43 (58.1)	4 (4.8)
Use of carbapenems in 3 months before first screening culture		23 (32.4)[d]	0 (0) [e]
Use of ESBL-selecting antibiotics in 3 months before first screening culture[b]		53 (74.6) [d]	4 (5.1) [e]
Relation to index patient	Partner		42 (50.6)
	Parent		19 (22.9)
	Child		11 (13.3)
	Sibling		11 (13.3)
Any positive isolate during study		49 (66.2)	34 (41.0)
ESBL-positive isolate at first screening culture		39 (52.7)	17 (20.5)
ESBL gene at first screening culture	CTX-M-1	5 (12.8)	1 (5.9)
	CTX-M-9	7 (17.9)	1 (5.9)
	CTX-M-14	3 (7.7)	2 (11.8)
	CTX-M-15	18 (46.2)	10 (58.8)
	CTX-M-27	1 (2.6)	0 (0)
	CTX-M-55/79	2 (5.1)	1 (5.9)
	SHV-2	0 (0)	1 (5.9)
	SHV-12	3 (7.7)	0 (0)
	TEM-19	0 (0)	1 (5.9)
Species at first screening culture[c]	*Escherichia Coli*	26 (66.7)	13 (76.5)
	Klebsiella pneumoniae	7 (17.9)	3 (17.6)
	Enterobacter Cloacae	5 (12.8)	1 (5.9)
	Citrobacter freundii	1 (2.6)	

ESBL, extended-spectrum β-lactamase; IQR, interquartile range.
[a] Data from one household contact were missing.
[b] Including cephalosporins, β-lactam/β-lactamase inhibitor combinations, or penicillins.
[c] When not available ($n = 17$), species from clinical culture was taken. In only 1/21 cases where species were both determined from the clinical culture and the culture at T0, there was disconcordance.
[d] Data from three index patients were missing.
[e] Data from four (extra) household contacts were missing.

Table 2
Culture results of index patients and household contacts

	During hospitalization of index patient (T0)	T3	T6	T12	T18
Included families	32	32	30	22	18
ESBL-positive index patients	32 (100%)	21[a] (67.7%)	18[b] (64.3%)	11 (50.0%)	7 (38.9%)
Included household contacts	53	53	48	36	32
ESBL-positive household contacts	16 [b] (31.4%)	16 [c] (32.0%)	10[a] (21.3%)	7 [c] (21.2%)	6 [d] (21.4%)
ESBLs related to index patient	13	13	8	5	6
Acquisitions of ESBLs related to index patient	0	5	4	1	1

ESBL, extended-spectrum β-lactamase.
[a] One culture was missing.
[b] Two cultures were missing.
[c] Three cultures were missing.
[d] Four cultures were missing.

The estimated probability of transmission of ESBL-producing bacteria from an index patient to a household contact, given that this contact did not acquire carriage through another route, was 67% (95% CI 38–88) and from a household member to another household member (including the index patient) was 37% (95% CI 12–71). This suggests that transmission originating from the index patient is the dominant route in the household dynamics of ESBL-producing bacteria, because of the longer duration of colonization.

Population model estimates

The parameters for the population model are given in Table 3. A weighted average acquisition rate was calculated for travel-associated acquisition based on Paltansing *et al.* [19] and travel data from the CBS (see Supplementary material, Information S5). In addition, the current prevalence of ESBLs in an unselected Dutch population was estimated to be 4%, based on the weighted average of van Hoek *et al.* [30] and G. van den Bunt (unpublished data). Hospital acquisition was set to 1.5%, based on the difference in admission and discharge ESBL-prevalence in 14 Dutch hospitals (M. Kluytmans-van den Bergh, unpublished data).

Under the assumption of absence of transmission between households, the steady-state prevalence in the baseline model was 1.6%, indicating that acquisitions during hospital admissions, during travel, and resulting from within-household transmission were not sufficient to reach the currently observed prevalence of 4%. To reach a steady-state prevalence of 4%, two options were evaluated: adding between-household transmission as a source for ESBL

Table 3
Parameter values used in the population model

	Symbol	Value
Acquisition rate in hospital	α_1	0.0000037/day[a]
Acquisition rate after travel	α_2	0.000082/day[b]
Within-household transmission rate	β	0.0053/colonized person/day
Decolonization rate hospital-acquired ESBL	γ_1	0.0026/day
Decolonization rate healthy persons	γ_2	0.0090/day
Total population	N	16 566 961 persons

ESBL, extended-spectrum β-lactamase.
[a] 9.1 admissions per 100 persons per year [28] multiplied by 1.5% acquisition/365 days.
[b] Acquisition rates from Paltansing *et al.* [19] together with travel data from the CBS [29] were used to obtain a weighted average acquisition rate (see Supplementary material, Information S5).

acquisition in the population or adding a constant external source for ESBL acquisition. The between-household transmission rate needed to be 0.67 times the within-household transmission rate to reach a prevalence of 4% (in the absence of the unknown external source). In the absence of between-household transmission, the acquisition rate originating from the unknown external source should be 0.00014 per day to reach the 4% prevalence. In that scenario, 5.1% of the population would acquire ESBLs from an external source per year. The relative contributions of the different sources are depicted in Fig. 1. Within-household transmission contributes for an estimated 14%–35% to the currently observed prevalence.

As a sensitivity analysis, we changed the proportion of people acquiring ESBLs in the hospital to 4%. This slightly changed the above numbers, but was still not enough to explain the current prevalence.

Discussion

This study demonstrated a high transmission rate of ESBL-producing bacteria within household settings, associated with a high prevalence of carriage of ESBL-producing bacteria in household members of patients identified as ESBL carriers during hospitalization. The results of a simple population model indicate that, apart from unknown sources and the minimal contribution of acquisition in healthcare settings, ESBL acquisition during travel and dispersion in the community may significantly contribute to the observed endemicity of ESBL carriage.

During our study more than 20% of household contacts were carriers of ESBL-producing bacteria at every time-point. This prevalence is considerably higher than the 8% found at hospital admission [31] and the estimated 4% in the general population in the Netherlands. Furthermore, according to the model, only 52% of the index patients appeared colonized in the gut at T0, whereas they were selected based on a clinical culture suspected of ESBL production. This can be explained by the fact that some clinical cultures did, in retrospect, not contain ESBL genes, some patients were admitted to the intensive care unit and received selective digestive decontamination, or patients received carbapenems to treat the ESBL infection, which might have influenced the yield of ESBL-producing bacteria in the screening culture. Also, some patients might have lost colonization before the screening culture was taken. As a consequence, some included families had no ESBL carriers during follow up. As they cannot contribute to transmission, they will also not impact the estimate of the transmission parameter.

Thirteen household contacts were colonized with genetically related ESBL-producing bacteria at the time of identification of an index patient. It seems unlikely that this carriage resulted from transmission from the index patient during the hospital stay. It seems more likely that the index patient and household contact were already colonized with the ESBL-producing bacteria before hospital admission of the index patient, e.g. from transmission within the household or from other sources [21]. At inclusion, especially ESBL-*E. coli* were isolated in index patients and household contacts (66.7% and 76.5%, respectively). These findings fit with the concept of community-spread [32]. Most of the model results will therefore be determined by the most prevalent strain

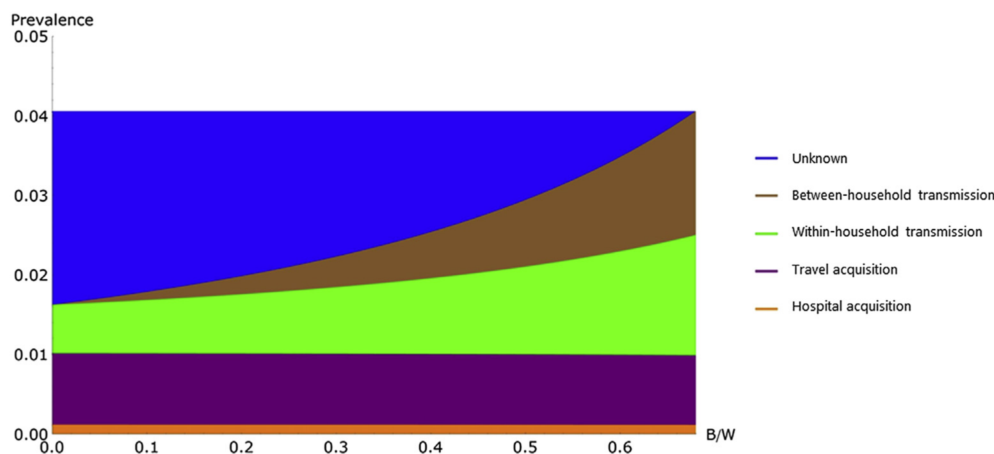

Fig. 1. Prevalence and relative contributions of hospital acquisition, travel acquisition, within-household transmission, and between-household transmission to the prevalence of extended-spectrum β-lactamase (ESBL). B/W, between-household transmission rate defined as a fraction of the within-household transmission rate. The coloured areas indicate the relative contributions of the different ESBL sources on the modelled prevalence. 'Unknown' indicates the contribution of the hypothetical external source to reach a prevalence of 4%.

(*E. coli* with CTX-M-15). However, the model gives mean values for the parameters and since this is a prevalent strain in the Netherlands, it will represent the current situation.

Our findings support the results from previous studies, in which 17%–32% of household contacts of ESBL carriers appeared colonized with genetically related ESBL-producing bacteria [7–11,13]. Also, the model estimated the median duration of colonization to be 9 months for index patients and only 2–3 months for household members. This is in line with several other studies assessing the duration of ESBL carriage [8,9,15–18].

Strengths of our study were the assessment of the colonization status in household contacts before hospital discharge of the index patient, the protocolled data collection from index patients and household contacts at fixed time-points, and the analysis of plasmid transfer among different *Enterobacteriaceae* species by performing transformations and PBRT [33]. Study limitations include the selection of patients. As inclusion of index patients and household contacts was based on the first screening culture being done during the admission of the index patient, there was a bias towards including patients with a longer length of stay, which might indicate more severely ill patients. This could have influenced the within-household acquisition rate if the illness severity increased the number of close contacts between household members. Moreover, this study was performed in three Dutch hospitals, which may reduce generalizability. Also, a number of households were lost to follow up. In at least 25% of the cases, death of the index patient was the reason for dropping out. Information on the cause of death was not collected, and it is, therefore, not clear if infection with ESBL-producing bacteria occurred. The other lost to follow-up events resulted from terminal illness of the index patients. Furthermore, we assumed that decolonization occurred with a similar rate in healthy household members of index patients and returning travellers. Yet, recent data suggest that this rate could be higher in healthy travellers [34], which would imply that the relative contribution of travellers was overestimated to some degree. Finally, the within-household model did not include, for example, detailed data on recent travel and antibiotic use which might have influenced the estimates of the model.

Based on the culture results we estimated a sensitivity of 74% of the screening process. Reasons for suboptimal screening included the self-sampling approach and the need to store samples before shipment through regular mail. Furthermore, the selection of a single colony may lead to an underestimation of transmission if a patient is carrying diverse ESBL types [35]. Finally, antibiotic use may have influenced test sensitivity, and possibly also transmission capacity and duration of colonization. The low sensitivity, however, suggests that a single negative faecal screening in this study is not sufficient to rule out persistent colonization.

For the population model we lacked sufficiently detailed data to make accurate estimations. Yet, based on the best data available for the Netherlands, the model suggests that there is not a single dominant acquisition route in the community. The model also demonstrated the importance of external acquisition in addition to the well-documented routes of nosocomial, within-household, and travel-associated acquisitions. This external acquisition route could be dominated by person-to-person transmission or by exogenous acquisition, for instance through selection of ESBL-producing bacteria after antibiotic treatment or contaminated foods or the environment [21]. The contribution of contaminated meat has been suggested as extensive by some [22,23] and as less prominent by others [36]. There are currently no estimates available on the person-to-person transmission rates outside healthcare settings and we still lack accurate estimates of the risks of contaminated meat products and environmental contamination. The modelling results clearly demonstrate the need to obtain these figures for a better understanding of the epidemiology of ESBL-producing bacteria.

Acknowledgements

An earlier version of this article was presented at ECCMID 2015, Abstract Reference No: ECCMD-0815.

Funding

This work was supported by the Netherlands Organization of Scientific Research (VICI NWO Grant 918.76.611 to M.J.M.B. and Priority Medicines Antimicrobial Resistance Grant 205100013 to M.R.H. and M.C.J.B.) and by funding from the European Community (RGNOSIS Integrated project [FP7/2007-2013] under grant agreement no. 282512 to M.R.H, M.C.J.B. and M.J.M.B.).

Transparency Declaration

The authors report no conflicts of interest.

Appendix A. Supplementary material

Additional Supporting Information may be found in the online version of this article at http://dx.doi.org/10.1016/j.cmi.2016.08.021.

References

[1] Oteo J, Pérez-Vázquez M, Campos J. Extended-spectrum β-lactamase producing *Escherichia coli*: changing epidemiology and clinical impact. Curr Opin Infect Dis 2010;23:320–6.
[2] Pitout JDD. Infections with extended-spectrum beta-lactamase-producing Enterobacteriaceae: changing epidemiology and drug treatment choices. Drugs 2010;70:313–33.
[3] Pitout JDD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis 2008;8:159–66.
[4] Cantón R, Novais A, Valverde A, Machado E, Peixe L, Baquero F, et al. Prevalence and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae in Europe. Clin Microbiol Infect 2008;14:144–53.
[5] Coque TM, Baquero F, Canton R. Increasing prevalence of ESBL-producing Enterobacteriaceae in Europe. Euro Surveill 2008;13:1–11.
[6] Reuland EA, Overdevest ITMA, al Naiemi N, Kalpoe JS, Rijnsburger MC, Raadsen SA, et al. High prevalence of ESBL-producing Enterobacteriaceae carriage in Dutch community patients with gastrointestinal complaints. Clin Microbiol Infect 2013;19:542–9.
[7] Hilty M, Betsch BY, Bögli-Stuber K, Heiniger N, Stadler M, Küffer M, et al. Transmission dynamics of extended-spectrum β-lactamase-producing enterobacteriaceae in the tertiary care hospital and the household setting. Clin Infect Dis 2012;55:967–75.
[8] Löhr IH, Rettedal S, Natås OB, Naseer U, Oymar K, Sundsfjord A. Long-term faecal carriage in infants and intra-household transmission of CTX-M-15-producing *Klebsiella pneumoniae* following a nosocomial outbreak. J Antimicrob Chemother 2013;68:1043–8.
[9] Tandé D, Boisramé-Gastrin S, Münck MR, Héry-Arnaud G, Gouriou S, Jallot N, et al. Intrafamilial transmission of extended-spectrum-β-lactamase-producing *Escherichia coli* and *Salmonella enterica* Babelsberg among the families of internationally adopted children. J Antimicrob Chemother 2010;65:859–65.
[10] Valverde A, Grill F, Coque TM, Pintado V, Baquero F, Cantón R, et al. High rate of intestinal colonisation with extended-spectrum-β-lactamase-producing organisms in household contacts of infected community patients. J Clin Microbiol 2008;46:2796–9.
[11] Rodríguez-Baño J, López-Cerero L, Navarro MD, Díaz de Alba P, Pascual A. Faecal carriage of extended-spectrum β-lactamase-producing *Escherichia coli*: prevalence, risk factors and molecular epidemiology. J Antimicrob Chemother 2008;62:1142–9.
[12] Strenger V, Feierl G, Resch B, Zarfel G, Grisold A, Masoud-Landgraf L, et al. Fecal carriage and intrafamilial spread of extended-spectrum β-lactamase-producing enterobacteriaceae following colonisation at the neonatal ICU. Pediatr Crit Care Med 2013;14:157–63.
[13] Lo WU, Ho PL, Chow KH, Lai EL, Yeung F, Chiu SS. Fecal carriage of CTX-M type extended-spectrum beta-lactamase-producing organisms by children and their household contacts. J Infect 2010;60:286–92.
[14] Sin MA, Takla A, Flieger A, Prager R, Fruth A, Tietze E, et al. Carrier prevalence, secondary household transmission, and long-term shedding in 2 districts

during the *Escherichia coli* O104:H4 outbreak in Germany, 2011. J Infect Dis 2013;207:432–8.

[15] Alsterlund R, Axelsson C, Olsson-Liljequist B. Long-term carriage of extended-spectrum beta-lactamase-producing *Escherichia coli*. Scand J Infect Dis 2012;44:51–4.

[16] Titelman E, Hasan CM, Iversen A, Nauclér P, Kais M, Kalin M, et al. Faecal carriage of extended-spectrum β-lactamase-producing Enterobacteriaceae is common 12 months after infection and is related to strain factors. Clin Microbiol Infect 2014;20:O508–15.

[17] Birgand G, Armand-Lefevre L, Lolom I, Ruppe E, Andremont A, Lucet JC. Duration of colonisation by extended-spectrum β-lactamase-producing Enterobacteriaceae after hospital discharge. Am J Infect Control 2013;41: 443–7.

[18] Zahar JR, Lanternier F, Mechai F, Filley F, Taieb F, Mainot EL, et al. Duration of colonisation by Enterobacteriaceae producing extended-spectrum β-lactamase and risk factors for persistent faecal carriage. J Hosp Infect 2010;75:76–8.

[19] Paltansing S, Vlot JA, Kraakman MEM, Mesman R, Bruijning ML, Bernards AT, et al. Extended-spectrum β-lactamase-producing Enterobacteriaceae among travelers from the Netherlands. Emerg Infect Dis 2013;19:1206–13.

[20] Kantele A, Laaveri T, Mero S, Vilkman K, Pakkanen SH, Ollgren J, et al. Antimicrobials increase travelers' risk of colonisation by extended-spectrum betalactamase-producing Enterobacteriaceae. Clin Infect Dis 2015;60:837–46.

[21] Ewers C, Bethe A, Semmler T, Guenther S, Wieler LH. Extended-spectrum β-lactamase-producing and AmpC-producing *Escherichia coli* from livestock and companion animals, and their putative impact on public health: a global perspective. Clin Microbiol Infect 2012;18:646–55.

[22] Leverstein-van Hall MA, Dierikx CM, Cohen Stuart J, Voets GM, van den Munckhof MP, van Essen-Zandbergen A, et al. Dutch patients, retail chicken meat and poultry share the same ESBL genes, plasmids and strains. Clin Microbiol Infect 2011;17:873–80.

[23] Kluytmans JAJW, Overdevest ITMA, Willemsen I, Kluytmans-van den Bergh MF, van der Zwaluw K, Heck M, et al. Extended-spectrum β-lactamase-producing *Escherichia coli* from retail chicken meat and humans: comparison of strains, plasmids, resistance genes, and virulence factors. Clin Infect Dis 2013;56:478–87.

[24] Voets GM, Leverstein-van Hall MA, Kolbe-Busch S, van der Zanden A, Church D, Kaase M, et al. International multicenter evaluation of the diversilab bacterial typing system for *Escherichia coli* and *Klebsiella* spp. J Clin Microbiol 2013;51:3944–9.

[25] Carattoli A, Bertini A, Villa L, Falbo V, Hopkins KL, Threlfall EJ. Identification of plasmids by PCR-based replicon typing. J Microbiol Methods 2005;63: 219–28.

[26] Centraal Bureau voor de Statistiek (CBS). Aantal particuliere huishoudens naar verschillende groottes, 1-1-2014 [Number of private households by different sizes, 1-1-2014]. Available on request from CBS.

[27] Ball F, Mollison D, Scalia-Tomba G. Epidemics with two levels of mixing. Ann Appl Probab 1997;7:6–89.

[28] Centraal Bureau voor de Statistiek (CBS). Medische contacten, ziekenhuisopname, medicijnen; pers.kenmerken, 2010–2013. [Medical contacts, hospital admissions, medicines; personal characteristics, 2010–2013]. Available from: http://statline.cbs.nl/StatWeb/publication/?VW=T&DM=SLNL&PA=81027NED&D1=a&D2=0-2&D3=0&D4=l&HD=110912-1014&HDR=G3,G2,G1&STB=T

[29] Centraal Bureau voor de Statistiek (CBS). Lange vakanties per land en werelddeel 2002–2013 [Long holidays per country and continent 2002–2013]. Available on request from CBS.

[30] Van Hoek AHAM, Schouls L, van Santen MG, Florijn A, de Greeff SC, van Duijkeren E. Molecular characteristics of extended-spectrum cephalosporin-resistant Enterobacteriaceae from humans in the community. PLoS One 2015;10:e0129085.

[31] Platteel TN, Leverstein-van Hall MA, Cohen Stuart JW, Thijsen SF, Mascini EM, van Hees BC, et al. Predicting carriage with extended-spectrum beta-lactamase-producing bacteria at hospital admission: a cross-sectional study. Clin Microbiol Infect 2015;21:141–6.

[32] Livermore DM. Current epidemiology and growing resistance of Gram-negative pathogens. Korean J Intern Med 2012;27:128–42.

[33] Woodford N, Turton JF, Livermore DM. Multiresistant Gram-negative bacteria: the role of high-risk clones in the dissemination of antibiotic resistance. FEMS Microbiol Rev 2011;35:736–55.

[34] Ruppé E, Armand-Lefèvre L, Estellat C, Consigny PH, El Mniai A, Boussadia Y, et al. High rate of acquisition but short duration of carriage of multidrug-resistant Enterobacteriaceae after travel to the tropics. Clin Infect Dis 2015;61:593–600.

[35] Stoesser N, Sheppard AE, Moore CE, Golubchik T, Parry CM, Nget P, et al. Extensive within-host diversity in fecally carried extended-spectrum beta-lactamase-producing *Escherichia coli*: implications for transmission analyses. J Clin Microbiol 2015;53:2122–31.

[36] De Been M, Lanza VF, de Toro M, Scharringa J, Dohmen W, Du Y, et al. Dissemination of cephalosporin resistance genes between *Escherichia coli* strains from farm animals and humans by specific plasmid lineages. PLoS Genet 2014;10:e1004776.