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Original Article

Household carriage and acquisition of extended-spectrum β-lactamase–producing Enterobacteriaceae: A systematic review

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Abstract

Objective: The epidemiology of ESBL-producing Enterobacteriaceae (ESBL-PE) has been extensively studied in hospitals, but data on community transmission are scarce. We investigated ESBL-PE cocarriage and acquisition in households using a systematic literature review.

Methods: We conducted a systematic literature search to retrieve cross-sectional or cohort studies published between 1990 and 2018 evaluating cocarriage proportions and/or acquisition rates of ESBL-PE among household members, without language restriction. We excluded studies focusing on animal-to-human transmission or conducted in nonhousehold settings. The main outcomes were ESBL-PE cocarriage proportions and acquisition rates, stratified according to phenotypic or genotypic assessment of strain relatedness. Cocarriage proportions of clonally related ESBL-PE were transformed using the double-arcsine method and were pooled using a random-effects model. Potential biases were assessed manually.

Results: We included 13 studies. Among 863 household members of ESBL-PE positive index cases, prevalence of ESBL-PE cocarriage ranged from 8% to 37%. Overall, 12% (95% confidence interval [CI], 8%–16%) of subjects had a clonally related strain. Those proportions were higher for *Klebsiella pneumoniae* (20%–25%) than for *Escherichia coli* (10%–20%). Acquisition rates of clonally related ESBL-PE among 180 initially ESBL-PE–free household members of a previously identified carrier ranged between 1.56 and 2.03 events per 1,000 person weeks of follow-up. We identified multiple sources of bias and high heterogeneity (I^2, 70%) between studies.

Conclusions: ESBL-PE household cocarriage is frequent, suggesting intrafamilial acquisition. Further research is needed to evaluate the risk and control of ESBL-PE household transmission.

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The prevalence of extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-PE) in the general population has now reached endemic levels in most countries.[1] This is worrisome because ESBL-PE are frequent causes of difficult-to-treat infections, with substantial health and economic burdens.[2]

ESBL-PE may spread by transfer of bacteria or mobile genetic elements. Some biologically fit phylogenetic groups particularly drive the emergence and persistence of virulence traits and acquisition of ESBL-PE.[3] Persistence of ESBL-PE in the community might be further amplified by various risk factors such as antibiotic exposure,[4–7] previous hospitalization,[5,8] recurrent urinary tract infection,[5] travel activities,[8,9] having children attending daycare centers,[10] as well as chicken meat consumption.[11] Overcrowded households also appear to increase the risk of ESBL-PE carriage.[12] Furthermore, intrahousehold transmission may play an important but understudied role. Several studies have shown that antibiotic-susceptible and -resistant *Escherichia coli* are transmitted between household members,[13] suggesting that both susceptible and resistant Enterobacteriaceae compete for niches within the gastrointestinal tract. This competitive balance is influenced by multiple factors including antibiotic exposure, which favors resistant Enterobacteriaceae and their intrahousehold transmission.[4]

Despite the potential relevance of ESBL-PE cross transmission among household members on persistence and spread of ESBL-PE in the community, evidence on this topic is scarce. We therefore aimed to systematically review epidemiological studies on ESBL-PE cocarriage and acquisition among household members.

Methods

Data sources and search strategy

We searched the Cochrane Library, PubMed, Embase and CINAHL databases for observational studies published between January 1990 and June 2018, without language restriction. Systematic manual

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reference search was performed from eligible articles' bibliography. Duplicate studies with the same title and authors were automatically deleted by the «Distiller» SR software (Evidence Partners, Ottawa, Canada). Core search strings, assembled Boolean operators, included "household OR community OR family OR outpatient" and "animal OR pet" for the study population; "extended-spectrum beta-lactamase OR lactamase OR cephalosporin OR beta-lactam resistance" for exposures; and "transmission OR carriage OR acquisition OR colonization OR microbiota OR molecular epidemiology" for outcomes. The full search strategies are available in the Supplementary Appendix online. This study was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) and Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statements.[14]

Selection criteria and definitions

This systematic review includes cohort or cross-sectional studies evaluating cocarriage proportions and acquisition rates of ESBL-PE in households, focusing mainly on intestinal carriage of *E. coli* and *Klebsiella pneumoniae*. ESBL-PE were defined phenotypically by presence of third-generation cephalosporin resistance and a positive double-disk synergy test, and/or genotypically by an identified ESBL-PE resistance gene. Studies were eligible if they included isolates sampled from human subjects. Cocarriage was defined as simultaneous carriage by 2 or more household members of a related ESBL-PE strain at a certain point in time or during a predefined follow-up period. Acquisition was defined as newly identified carriage of a related strain in another household member who was previously ESBL negative. Relatedness definition depended on the level of microbiological discrimination employed. Cocarriage and acquisition rates were stratified considering the level of microbiological discrimination: "closely related" pathogens were phenotypically similar bacteria, sharing the same phenotypic or genotypic resistance profile, and "clonally related" pathogens were bacteria assessed for relatedness through genotyping methods.

Studies were stratified according to their sampling scheme. In index-case–based studies (category A), recruitment of families derived from a previously identified ESBL-PE index case. In population-based studies (category B), household members were not recruited based on a previously known index case but from the general population. In category A, cocarriage proportions were calculated as the number of household members of a colonized or infected index case simultaneously carrying a closely related or clonally related ESBL-PE, among the total number of household members (excluding the index case). In category B, all household members presenting simultaneous ESBL-PE–related carriage among the total number of household members were considered (Fig. 1).

We excluded single-household case reports, studies focusing on animal-to-animal or animal-to-human transmission only, as well as studies focusing on the environment (eg, surface water) or conducted in nonhousehold settings (eg, childcare facilities). Studies focusing on international travelers, indigenous populations with a specific way of living, farms, or foodborne community outbreaks were excluded. Due to specific exposures and an extensive literature on the topic, studies on mother-to-newborn transmission were also excluded.

Study screening and data extraction

Title and abstract screening was performed independently by 2 authors (R.M. and M.E.R.). All discrepancies were solved by consensus, involving a third investigator (M.A.) if needed. Concordance

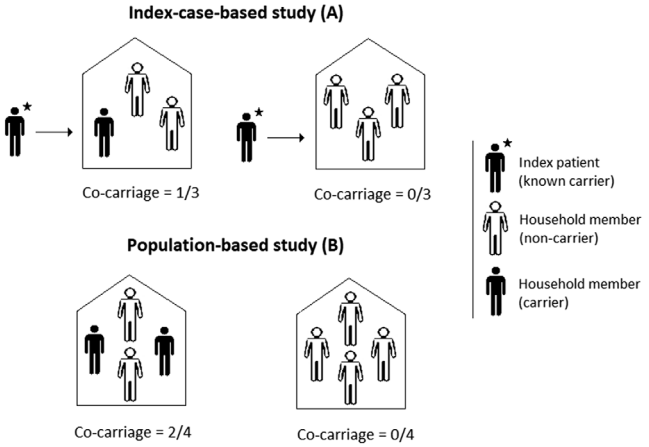

Fig. 1. Examples for the evaluation of cocarriage estimates in studies based on their sampling schemes.

was checked by Cohen's κ coefficient. One author (R.M.) performed full-text screening and data extraction, with any uncertainties resolved by discussion with another author (M.E.R.). We extracted the following data: study characteristics (study dates, design, outcomes, and follow-up), study population (ie, characteristics of index cases and families, number of household members, and potential biases addressed), and microbiological methods. As the primary outcome, ESBL-PE cocarriage proportions and acquisition rates were calculated based on available information. Preferably, cocarriage proportions of longitudinal studies were generated at baseline as a point prevalence to compare them with cross-sectional studies. However, if no such information was available, cocarriage proportions of the overall follow-up period were reported as a period prevalence. Both study screening and data extraction were performed using standardized electronic forms in DistillerSR software (Evidence Partners, Ottawa, Ontario, Canada). Potential clinical and microbiological confounders were specifically reported, both for index cases and their household members. Characteristics of household members, sampling methods, loss to follow-up, hospital stay, antibiotic exposure, travel activity, food intake, daycare centers, and socioeconomic status were considered clinically relevant. The number of colonies analyzed per morphotype and the use of broth enrichment were considered microbiologically relevant.

Statistical analysis

The main outcomes of interest were the proportion of cocarriage and rate of acquisition among household members, stratified by the study type (defined by its sampling scheme), and microbiological discrimination level. Cocarriage proportions of closely related and clonally related Enterobacteriaceae were compared. Cocarriage proportions of household members with clonally related ESBL-PE from index-case–based studies were pooled using meta and metafor packages.[15,16] Double-arcsine transformation was applied on raw proportions to estimate a normal distribution before pooling.[17] Transformed individual effect sizes were then pooled using a random-effects model to account for between-study variance. Heterogeneity among effect size was estimated using the Q test and the I^2 test. Subgroup comparisons were performed to explore relationships and heterogeneities by stratifying individual-based cocarriage among the proportion of species isolated from index cases (ie, >15% or <15% of *K. pneumoniae*). Potential publication bias or small-study effects were examined by funnel plot. All analyses were performed using the R open-source software environment,

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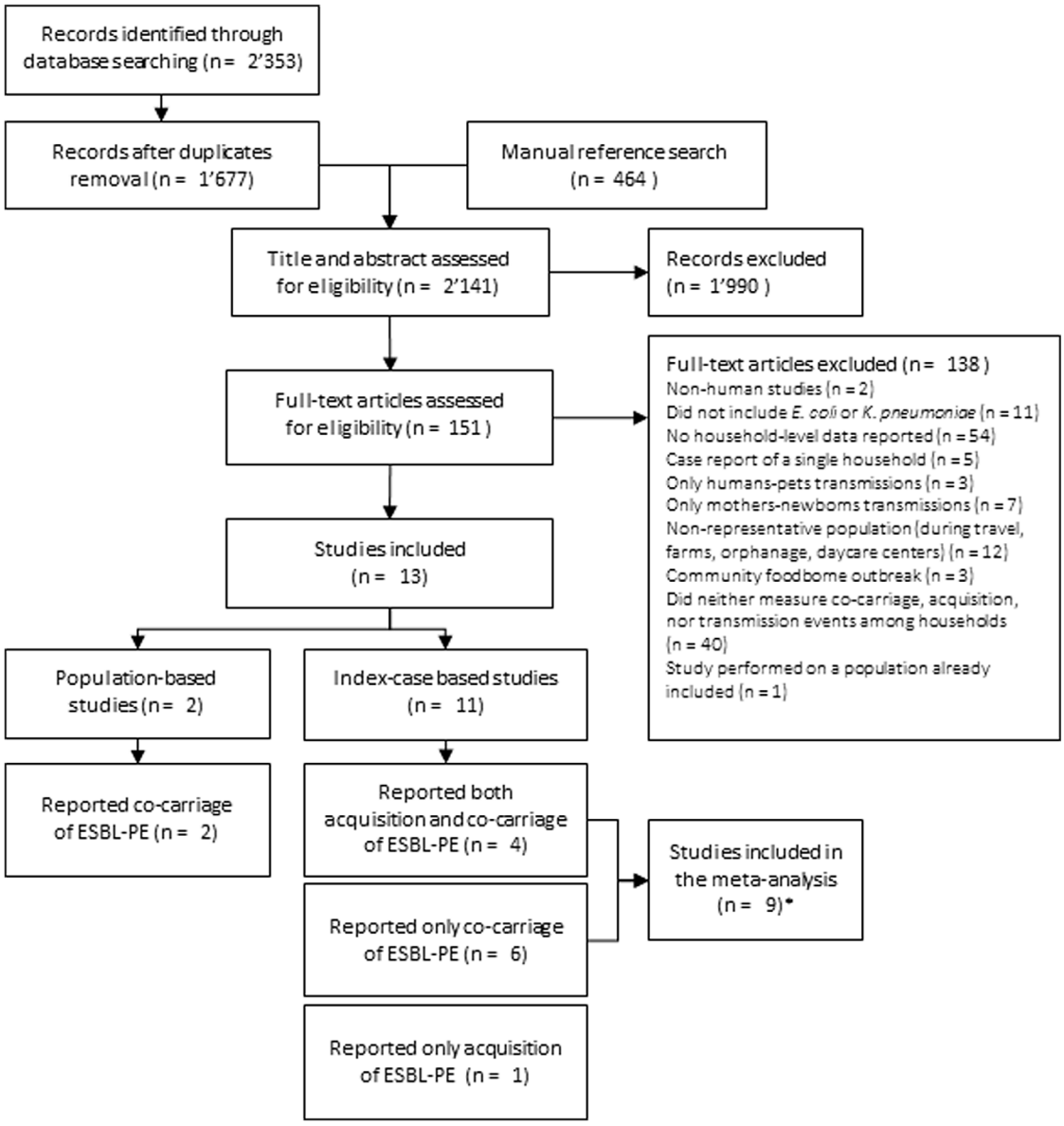

Fig. 2. Systematic review flow chart detailing the study selection procedure. Note. *Only studies evaluating cocarriage of clonally related extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-PE) were included in the meta-analysis.

version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria). The R code is available in the Appendix (online).

Results

Study selection and features of included studies

The literature search identified 2,353 articles. After duplicate removal, 2,141 articles were screened for eligibility. In total, 151 articles underwent full-text screening (κ, 0.80). Finally, 13 studies[4,18–29] were selected for data extraction and bias assessment (Fig. 2). Two publications initially classified as population-based studies qualified as index-case studies because we were able to extract household cocarriage and acquisition rates with at least 1 colonized member from the crude data.[4,22] Thus, sampling schemes were population based and index-case based for 2 and 11 studies, respectively. The 2 population-based studies were considered cross sectional,[21,25] and of the 11 index-case–based studies, 7 were longitudinal cohort studies[4,20,24,26–29] and 4 were cross-sectional studies.[18,19,22,23] Two longitudinal studies were considered as nested cross-sectional studies for the purpose of our review because after a first baseline sampling at home, subsequent follow-up occurred only in a hospital setting.[18,25] Cocarriage data were not collected for one index-case–based study that only included previously negative household members.[24] Another index-case–based study reporting only cocarriage of closely related bacteria[4] was excluded from the meta-analysis, which focused on only those 9 studies with data on cocarriage of clonally reported pathogens. Acquisition rates were extracted and calculated from 5 of the 7 index-case–based cohort studies, excluding 2 studies with unknown ESBL-PE status of household members at baseline.[20,29]

Study population

The main characteristics of the included studies are displayed in Table 1. For index-case–based studies, sample sizes ranged from

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Table 1. Study Population and Characteristics of Included Studies

Bibliography	Country	ESBL spp Isolated *(For the index cases if not specified)*	Follow-up Duration	Category of Participants	ESBL-PE Status at Inclusion	Population Size	Age, Median (IQR)	Female Gender, No. (%)	Cocarriage Considered
Crossover population-based studies without index cases									
Lo WU, et al 2010[21]	China	81% *Escherichia coli*, 19% *Klebsiella pneumoniae (among all participants)*	NA	First group of household members	Unknown	53	2 y (0.8–3)	21 (40)	Closely related: CTXM-PE Clonally related: CTXM strain
				Second group of household members	Unknown	172	5 y (29 infants) (2.3–8) 35 y (143 adults) (31–43)	104 (60)	
Kurz MS, et al 2017[25]	Rwanda	48% *E. coli*, 36% *K. pneumoniae*, 16% *Enterobacter cloacae (among the first group of household members)*	NA	First group of household members[a]	Unknown	392	29 y (range, 0–94)	252 (64)	Closely related: ESBL-PE partially concordant
				Second group of household members[a]	Unknown	361	36 y (range, 10–76)	289 (80)	
Crossover index-case–based studies									
Rodriguez-Bano J et al 2008[19]	Spain	100% *E. coli*	NA	Index cases (*outpatients*)	Identified infection	53[b]	69 y (52–75)	37 (70)	Closely related: ESBL spp Clonally related: ESBL strain
				Household contacts	Unknown	73	43 y (23–63)	41 (56)	
Valverde A et al. 2008[23]	Spain	99% *E.coli*, 1% *K. pneumoniae*	NA	Index cases (*outpatient*)	Identified infection	40	63.6 y (mean) (range, 2–96)	34 (85)	Closely related: ESBL spp Clonally related: ESBL strain
				Household contacts	Unknown	54	NA	NA	
Adler A et al 2014[18]	France, Italy, Spain, Israel	43% *E. coli*, 27% *K. pneumonia*, 16% *P. mirabilis*, 6% *Citrobacter* spp, 5% *Enterobacter* spp, 3% others	NA	Index cases (*inpatient*)	Known colonization	194	65.9 y (mean) (range: 18–99)	98 (50)	Closely related: ESBL spp Clonally related: ESBL strain
				Household contacts	Unknown	286	52 y (42.7–60.2)	204 (71)	
Liakopoulos A et al 2018[22]	The Netherlands	93.7% *E. coli*, 3.75% *K. pneumoniae*, 2.5% *E. cloacae*	NA	First group of household members[c]	Known colonization	66	2.4 y (1.5–3.3)	NA	Closely related: ESBL spp sharing the same resistance genes Clonally related: ESBL strain
				Second group of household members[c]	Unknown	66	34 y (31–37)	NA	
Longitudinal index-case–based cohort studies									
Tande D et al 2010[26]	France	56% *E. coli*, unknown proportion of *S. enterica*	12 mo (period prevalence)	Index cases (*outpatient, post-adoption*)	Known colonization	22	NA	NA	Closely related: ESBL-PE Clonally related: ESBL strain
				Household contacts	Unknown	49	NA	NA	
Hilty M et al 2012[29]	Switzerland	88% *E. coli*, 12% *K. pneumoniae*	12 mo (period prevalence[d])	Index cases (*inpatient & outpatient*)	Known colonization or infection	82	49 y (mean)	52 (63)	Closely related: ESBL-Ec and ESBL-Kp Clonally related: ESBL strain
				Household contacts	Unknown	96	NA	NA	

(*Continued*)

Table 1. (*Continued*)

Bibliography	Country	ESBL spp Isolated *(For the index cases if not specified)*	Follow-up Duration	Category of Participants	ESBL-PE Status at Inclusion	Population Size	Age, Median (IQR)	Female Gender, No. (%)	Cocarriage Considered
Löhr IH et al 2013[27]	Norway	100% *K. pneumoniae*	23 mo (period prevalence)	Index cases (*inpatient, post-outbreak*)	Known colonization	28	Neonates	26 (51)	Closely related: CTXM-15 spp Clonally related: CTXM-15 strain
				Household contacts	Unknown	60	NA	NA	
Strenger V et al 2013[20]	Austria	44% *K. oxytoca*, 28% *S. marcescens*, 24% *K. pneumoniae*, 4% *E. coli*	12 mo (period prevalence[d])	Index cases (*inpatient*)	Known colonization	25	Neonates	13 (52)	Closely related: ESBL-PE Clonally related: ESBL strain
				Household contacts	Unknown	49	NA	NA	
Arcilla MS et al 2017[24]	The Netherlands	Enterobacteriaceae *(no detail)*	12 mo (not considered for cocarriage)	Index cases (*outpatient, returning travelers*)	Known colonization	152	NA[e]	NA[e]	Closely related: ESBL-PE sharing the same group of resistance gene
				Household contacts	Not colonized by ESBL-PE	168	NA[e]	NA[e]	
Haverkate MR et al 2017[28]	The Netherlands	66,7% *E. coli*, 17.9% *K. pneumoniae*, 12.8% *E. cloacae*, 2.6% *Citrobacter freundii*	18-mo period (closely related) prevalence and point (clonally related ESBL PE) prevalence	Index cases (*inpatient*)	Suspicion of colonization or infection	74	54 y (mean) (SD, 24)	36 (49)	Closely related: ESBL-PE Clonally related: ESBL strain
				Household contacts	Unknown	84	43 y (mean) (SD, 23)	45 (54)	
Stewardson AJ et al 2018[4]	Belgium, Poland, Switzerland	100% *E. coli*	36 d (point prevalence)	Index cases considered for cocarriage[f]	Known colonization	33	30 y (19–55)	21 (64)	Closely related: ESBL spp
				Household contacts considered for cocarriage[f]	Unknown	46	39 y (27.2–49)	26 (56)	
				Index cases considered for acquisition rates[f]	Known colonization	36	NA[e]	NA[e]	
				Household contacts considered for acquisition rates[f]	Free of ESBL-PE at baseline	55	NA[e]	NA[e]	

Note. CTXM, specific family of genes coding for extended-spectrum β-lactamase; CTXM-15, specific gene coding for extended-spectrum β-lactamase; ESBL, extended-spectrum β-lactamase; ESBL-PE, extended-spectrum β-lactamase–producing Enterobacteriaceae; ESBL Ec, extended-spectrum β-lactamase–producing *Escherichia coli*; ESBL Kp: extended-spectrum β-lactamase–producing *Klebsiella pneumoniae*.

[a]Caregivers and not household members were concerned.

[b]13 index cases lived alone.

[c]Data were extracted based on the crude microbiological data from the study "Van den Bunt et al." Epidemiological information on this subpopulation (household members of a known carrier) is missing.

[d]Longitudinal cohort study not considered for acquisition rates because unknown proportion of previously negative household members.

[e]Nested cohort from the main study population, with missing epidemiological information.

[f]Cocarriage: 1 household member positive at baseline per household. Acquisition rates: 1 household member positive with negative household members.

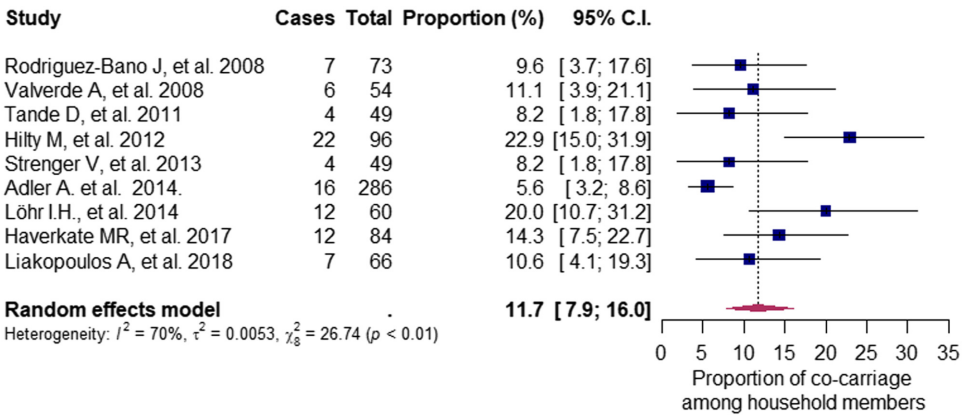

Fig. 3. Forest plots for prevalence of cocarriage of clonally related extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-PE).

46 to 286 household members, and for population-based studies, sample sizes ranged from 225 to 753 household members. The 9 studies based on index cases defined them by being colonized[18,20,24,26,27] or infected[19,23] with ESBL-PE or both.[28,29] The 4 population-based studies recruited household members from inpatient,[21,25] outpatient,[4,21] or healthy community settings.[22] Of the 13 studies, 3 recruited an entire family[21,26,28] and 10 recruited a convenience sample of at least 2 household participants.[4,18–20,22–25,27,29]

Cocarriage proportions or acquisition rates were assessed for closely related and for clonally related pathogens in 13 of 13 and 10 of 13 studies, respectively. Closely related pathogens were defined as the sharing of same ESBL-PE species,[4,18,19,22,23,27,29] or ESBL-PE without species identification.[20,21,24–26,28] Pathogen characteristics, as well as main features of the applied microbiologic methods are described in Supplementary Table 1 (online). Supplementary Table 2 (online) summarizes reporting practices of the included studies. Potential confounders and biases were mainly reported for index cases at baseline, especially for previous antibiotic intake (12 of 13 studies) and previous hospital stays (10 of 13 studies). However, risk factors were often heterogeneously defined, and poorly reported during follow-up of household members. Considering potential microbiological biases (Supplementary Table 3 online), only 3 studies used broth enrichment,[22,24,27] and 4 analyzed >1 colony per morphotype.[4,19,21,22]

Index-case–based studies evaluating cocarriage of ESBL-producing Enterobacteriaceae among household members

Cocarriage proportions of closely related pathogens were collected as a point prevalence (either in cross-sectional studies or at baseline of longitudinal studies) in 5 studies and as a period prevalence (with varying follow-up from 12 to 23 months) in 5 longitudinal studies. When considering cocarriage of closely related pathogens at the species level, point prevalence of ESBL-PE cocarriage among household members of a previously identified index case ranged between 8% and 27% and period prevalence ranged between 14% and 34%. When considering cocarriage of closely related pathogens at the Enterobacteriaceae level, period prevalence of cocarriage among household members of an index case ranged between 18% and 37%.

In the 9 studies assessing cocarriage of clonally related pathogens, including 817 household members of index cases colonized or infected by ESBL-PE, the proportion of cocarriage with a clonally related strain ranged between 5.6% and 23% (cf, Supplementary Table 4 online). The pooled estimate was 12% (95% confidence interval [CI], 8%–16%) (Fig. 3). High heterogeneity was observed among studies (I^2, 70%), with a Q test for heterogeneity rejecting the hypothesis of homogeneity ($P < .001$).

Cocarriage proportions of clonally related *K. pneumoniae* was evaluated in 2 studies and ranged between 20% and 25%[27,29]; cocarriage proportions of clonally related *E. coli* was evaluated in 3 studies and ranged between 10% and 20%.[19,23,29] These findings reveal important differences after stratification by species. In a subgroup analysis stratifying studies that included <15% versus >15% of index cases colonized by ESBL-producing *Klebsiella* spp, cocarriage proportions were observed to increase for studies including more *Klebsiella* spp (13% [95% CI, 7%–21%] vs 10% [95% CI, 6%–14%]). Inspection of the funnel plot (Fig. 4) was not suggestive of any reporting bias for the primary outcome.

Population-based studies evaluating cocarriage of ESBL-producing Enterobacteriaceae among multiple families

Cocarriage at the population level was evaluated by 2 studies for closely related ESBL-PE (prevalence, 15% and 14%) and by a single study for clonally related ESBL-PE (6%; Supplementary Table 5 online).

Acquisition rates of ESBL-PE

Follow-up periods in the 5 prospective cohort studies evaluating ESBL-PE acquisition rates ranged from 36 days to 23 months, with a variable frequency between screening time points. Acquisition rates of closely related ESBL-PE among household members of a previously identified carrier were reported by 2 studies and ranged between 1.5 and 17.39 events per 1,000 person weeks, via follow-up of 223 initially ESBL-PE–free household members. When we restricted the analysis to clonally related ESBL-PE reported in 3 studies, the rates ranged between 1.56 and 2.03 events per 1,000 person weeks of follow-up among 180 initially ESBL-PE–free household members (Supplementary Table 6 online). Acquisition rates were slightly higher when expressed as person weeks at risk, excluding the follow-up time after an acquisition of a related ESBL-PE. In the 3 studies providing detailed data on person time at risk, the corresponding rates ranged between 1.69 and 19.21 events per 1,000 person weeks at risk versus, respectively, 1.56 and 17.39 events per 1,000 person weeks of total follow-up.

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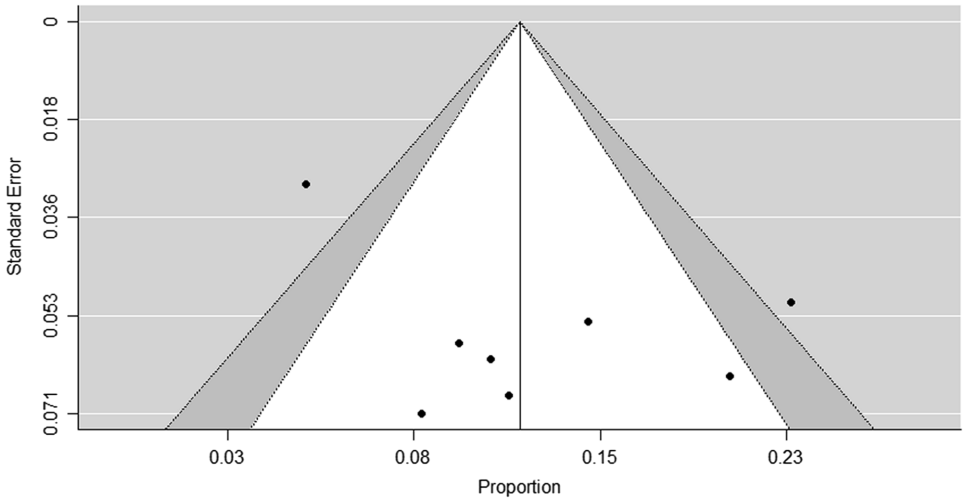

Fig. 4. Evaluation of potential publication bias, funnel plot for prevalence of cocarriage of clonally related extended-spectrum β-lactamase–producing Enterobacteriaceae (ESBL-PE).

Discussion

ESBL-PE spread dominates in the community setting, mainly driven by specific subclones of ESBL-producing *E. coli*.[30] Through the sharing of well-recognized risk factors for community ESBL-PE carriage[8–11] and through their daily proximity, household contacts of ESBL-PE carriers are at risk of ESBL-PE acquisition. Household transmission of ESBL-PE has been described, but knowledge of its extent remains scant. To our knowledge, this is the first systematic review performed on cocarriage and acquisition of ESBL-PE in private households.

Higher carriage proportions were observed among household members of a colonized or infected index case compared to ESBL-PE carriage prevalence in the general population. For instance, carriage of ESBL-producing *E. coli* and *K. pneumoniae* was 4.5% in the Dutch population[31] but was 18% among such household members.[22,28] In Switzerland, community carriage of ESBL-producing *E. coli* was 5.3%[32] but reached 34%[29] when considering household members. In France and Spain, community carriage of ESBL-producing *E.coli* was between 2% and 7%,[33,34] but this rate was 14%–27% among household members.[19,23,26] When focusing on ESBL-producing *K. pneumoniae*, community carriage was 0.3%[35] in Norway, and 20% in household members of a colonized index case.[27] Thus, families and households may serve as ESBL-PE amplification platforms.

Cocarriage proportions decreased when considering only cocarriage of clonally related ESBL-PE, with a pooled prevalence of 12%. These findings underline the importance of genotyping methods to elucidate the epidemiology of ESBL-PE in household settings. Moreover, they suggest that multiple sources of ESBL-PE introduction (eg, food, travel) into households may exist beyond transmission via ESBL-PE index cases, which may explain the polyclonal ESBL-PE picture observed in many households.[36]

Confidence intervals of pooled proportions for clonally related pathogens, as well as the range of prevalence proportions and rates, suggest important variations in cocarriage and acquisition of ESBL-PE between household members. Unfortunately, considering the small sample size and number of studies, the risk of overfitting for subgroup analyses was high. However, several hypotheses might explain this heterogeneity. First, substantial differences existed in study populations, risk factors, and microbiological features. For instance, index cases with an ESBL-PE–related infection, recruitment after an outbreak with a particularly transmissible strain, as well as antibiotic exposure, may increase the likelihood of ESBL-PE cross transmission.[4] Additional characteristics of household members, such as healthcare exposure, travel activities, and food habits, may have influenced ESBL-PE acquisition risks.[4,5,10,11,24] Second, the various study designs led to different estimates. Cocarriage evaluated during cross-sectional studies and at baseline during longitudinal studies was considered a point-prevalence proportion. This contrasts with cocarriage evaluated during the whole follow-up of a cohort study, considered a period-prevalence proportion. Comparability of such proportions might be questionable and may have caused methodological heterogeneity.[37] Third, included studies originated from different regions of the world. However, European households were overrepresented; thus, acquisition rates and cocarriage proportions might differ in other settings, especially in low- and middle-income countries. Clearly, the geographic and socioeconomic context influences ESBL-PE colonization pressure, antibiotic exposure, way of living, proximity of household members and ultimately ESBL-PE household acquisition rates.

We identified multiple potential biases in the included studies. Several studies only included 2 members in household members, introducing selection bias and possibly missing transmission chains. At isolate levels, relatedness analysis was often performed on the basis of a unique isolate per morphotype to determine cocarriage of clonally related pathogens. Acknowledging coexistence of sensitive and resistant ESBL-PE in our microbiota, some related strains and thus cocarriage has possibly been missed. Another detection bias might have missed resistant pathogens in the absence of broth-based methods, in case of very low bacterial load. Finally, despite the genotyping performed in more than half of included studies, the applied methods were not discriminative enough to assess strain relatedness among isolates to distinguish acquisition from external sources versus cross transmission. Of upmost importance, none of the included studies performed advanced bacterial or plasmid sequencing using whole-genome sequencing to elucidate the exact transmission pathways of ESBL-PE, as is already done in hospital-based studies.[38] Only 3 studies examined the spread of plasmids to other species in the gut across family members in the absence of clonally related pathogens (Supplementary Appendix 7 online). However, the methods

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were not discriminative enough to ascertain horizontal transfers of mobile genetic elements. Only sporadic sharing of plasmid profiles among household members were observed, but available data were not sufficient to measure the influence of mobile genetic transfer in acquisition rates of antibiotic resistance.

Differences in cross-transmission risk between *Klebsiella* spp and *E. coli* have been described in hospital-based studies.[39] We identified a similar trend in the included household studies. If *Klebsiella* is more transmissible, *E. coli* seems to be a more successful colonizer of humans. This dominance might be explained by the presence of more transmission pathways (food chain, environment) and successful dissemination of particularly virulent subclones.[40]

In summary, the observed ESBL-PE cocarriage prevalence and acquisition rates are concerning and may explain in part ESBL-PE spread and persistence among families, along with other determinants. The observed heterogeneity in study designs and populations has contributed to the variability of results and limited the precision of our estimates. The methodological limitations of included studies therefore highlight the need for further research evaluating ESBL-PE cocarriage, acquisition, and cross transmission in households, with standardized selection and follow-up of participants. Furthermore, novel sequencing approaches are required to ascertain exogenous acquisition of bacteria and plasmids. Such research output could help to provide a broader understanding of ESBL-PE transmission dynamics in a One Health perspective, and ultimately could drive future preventive measures to control ESBL-PE in the community.

Supplementary material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2019.336

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