# **Supplementary material**

This appendix has been provided by the authors to provide readers additional information about this study.

Supplement to: “**Household carriage and acquisition of ESBL-producing Enterobacteriaceae: a systematic review.”**

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## Search concepts

Search concepts included in study type hedges were identified using the PICO format.

* Population:
* Household\*, communit\*, famil\*
* MeSH:
	+ Medline: household, community, family caregiver, household and family, outpatient
	+ Embase: 'family', 'community car', 'household', outpatient
	+ Cochrane: Family, Residence Characteristics, outpatient
* Animal\*
* MeSH:
	+ Medline: “Animals, Domestic”, Pets, "animal, companion"
	+ Embase: “companion animal”, “pet animal”
	+ Cochrane: Pets
* Exposure:
* ESBL, lactamase
* MeSH:
	+ Medline: cephalosporin beta lactamase, beta lactamase, cephalosporin resistance
	+ Embase: 'extended spectrum beta lactamase producing enterobacteriaceae', 'extended spectrum beta lactamase', ‘cephalosporin resistance’
	+ Cochrane: beta-Lactam Resistance
* Outcome:
* Transmiss\*, carriage, acquisition, coloniz\*, microbiota, molecular AND epidemiolog\*
* MeSH:
	+ Medline: communicable disease transmission, “disease transmission, infectious”, microbiota, molecular epidemiology
	+ Embase: 'microbial colonization', 'acquisition', 'disease transmission', microflora, risk factor, molecular epidemiology
	+ Cochrane: “Disease Transmission, Infectious”, Microbiota, Molecular Epidemiology
* Design: all types of observational studies were included

## Search strategy

For Medline the following terms were used:

|  |  |
| --- | --- |
| Search | Query |
| #6 | #3 AND #4 AND #5 (filter 1990-2018)(no filter about HUMAN studies because might discard some pertinent studies (SATURN)) |
| #5 | (ESBL OR lactamase OR cephalosporin beta lactamase[MeSH Terms] OR beta lactamases[MeSH Terms] OR cephalosporin resistance[MeSH Terms]) |
| #4 | (Transmiss\* OR carriage OR acquisition OR coloniz\* OR microbiota OR molecular epidemiolog\* OR communicable disease transmission[MeSH Terms] OR disease transmission, infectious[MeSH Terms] OR microbiota[MeSH Terms] OR molecular epidemiology[MeSH Terms]) |
| #3 | #1 OR #2 |
| #2 | (Animal\* OR animal, domestic[MeSH Terms] OR pets[MeSH Terms] OR animal, companion[MeSH Terms]) |
| #1 | (Household\* OR communit\* OR famil\* OR household[MeSH Terms] OR community[MeSH Terms] OR family caregiver[MeSH Terms] OR household and family[MeSH Terms]) |

For EMBASE the following search strategy was used (after a search for index terms of relevant records):

No. Query Results

#31. #12 AND #18 AND #30 (filter 1990-2018 + embase)

#30. #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29

#29. 'molecular epidemiology'/exp

#28. 'microflora'/exp

#27. 'disease transmission'/exp

#26. 'acquisition'/exp

#25. 'microbial colonization'/exp

#24. 'molecular epidemiolog\*':ti,ab,kw

#23. 'microbiota':ti,ab,kw

#22. 'coloniz\*':ti,ab,kw

#21. 'acquisition':ti,ab,kw

#20. ‘carriage’:ti,ab,kw

#19. 'transmiss\*':ti,ab,kw

#18. #13 OR #14 OR #15 OR #16 OR #17

#17. 'extended spectrum beta lactamase'/exp

#16. 'extended spectrum beta lactamase producing enterobacteriaceae'/exp

#15. ‘cephalosporin resistance’/exp

#14. 'lactamase':ti,ab,kw

#13. 'esbl':ti,ab,kw

#12. #7 OR #11

#11. #8 OR #9 OR #10

#10. ‘companion animal’/exp

#9. ‘pet animal’/exp

#8. ‘animal\*’:ti,ab,kw

#7. #1 OR #2 OR #3 OR #4 OR #5 OR #6

#6. 'family'/exp

#5. 'famil\*':ti,ab,kw

#4. 'community care'/exp

#3. 'communit\*':ti,ab,kw

#2. 'household'/exp

#1. 'household\*':ti,ab,kw

For the Cochrane database, the following MeSH terms were used :

ID Search

#1 "household\*":ti,ab,kw

#2 "communit\*":ti,ab,kw

#3 "famil\*":ti,ab,kw

#4 MeSH descriptor: [Family] explode all trees

#5 MeSH descriptor: [Residence Characteristics] explode all trees

#6 #1 or #2 or #3 or #4 or #5

#7 "animal\*":ti,ab,kw

#8 MeSH descriptor: [Pets] explode all trees

#9 #7 or #8

#10 #6 or #9

#11 "ESBL":ti,ab,kw

#12 "lactamase":ti,ab,kw

#13 MeSH descriptor: [Cephalosporin resistance] explode all trees

#14 MeSH descriptor: [beta-Lactam Resistance] explode all trees

#15 #11 or #12 or #13 or #14

#16 "transmiss\*":ti,ab,kw

#17 "acquisition":ti,ab,kw

#18 “carriage”:ti,ab,kw

#19 "coloniz":ti,ab,kw

#20 "microbiota":ti,ab,kw

#21 “molecular and epidemiolog\*”:ti,ab,kw

#22 MeSH descriptor: [Disease Transmission, Infectious] explode all trees

#23 MeSH descriptor: [Microbiota] explode all trees

#24 MeSH descriptor: [Molecular Epidemiology] explode all trees

#25 #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24

#26 #10 and #15 and #25 (1990 - 2018)

Importation of references:

All data were imported in DistillerSR using RIS format. Txt format for Central and Pubmed have been adapted in a RIS-friendly format by <https://eppi.ioe.ac.uk/cms/er4/RISExport/tabid/2934/Default.aspx>

Pilot-test of the search strategy:

The search strategy was pilot-tested with a subset of relevant studies:

<https://www.ncbi.nlm.nih.gov/pubmed/29331548>

Effect of outpatient antibiotics for urinary tract infections on antimicrobial resistance among commensal Enterobacteriaceae: a multinational prospective cohort study.

<https://www.ncbi.nlm.nih.gov/pubmed/27596534>

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

<https://www.ncbi.nlm.nih.gov/pubmed/18641033>

Faecal carriage of extended-spectrum beta-lactamase-producing Escherichia coli: prevalence, risk factors and molecular epidemiology.

<https://www.ncbi.nlm.nih.gov/pubmed/20233775>

Intrafamilial transmission of extended-spectrum-beta-lactamase-producing Escherichia coli and Salmonella enterica Babelsberg among the families of internationally adopted children.

<https://www.ncbi.nlm.nih.gov/pubmed/22718774>

Transmission dynamics of extended-spectrum β-lactamase-producing Enterobacteriaceae in the tertiary care hospital and the household setting.

<https://academic.oup.com/jac/article/72/2/589/2374137>

ESBL/AmpC-producing Enterobacteriaceae in households with children of preschool age: prevalence, risk factors and co-carriage

<https://www.ncbi.nlm.nih.gov/pubmed/18562591>

High rate of intestinal colonization with extended-spectrum-beta-lactamase-producing organisms in household contacts of infected community patients.

<https://www.ncbi.nlm.nih.gov/pubmed/20144898>

Fecal carriage of CTXM type extended-spectrum beta-lactamase-producing organisms by children and their household contacts.

<https://academic.oup.com/jac/article/68/5/1043/682782>

Long-term faecal carriage in infants and intra-household transmission of CTX-M-15-producing Klebsiella pneumoniae following a nosocomial outbreak

|  |  |
| --- | --- |
|  | Relevant studies |
| Search strategy(Pubmed) | Studies retrieved  | 9 |
| Studies not retrieved | 0 |
|  | 9 |

Sensitivity of the search strategy: 100%

## Figures & tables

Supplementary table 1. Microbiological methods

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Bibliography** | **Sample** | **Broth** | **Species discrimination** | **Target pathogen or organism** **for the index case** | **Method of resistance determination**  | **Resistance profile included**  | **Technique used to assess relatedness** |
| Rodriguez-Bano J et al. 2008 19 | rectal swab | no | genotypic | 100% *E. coli* | genotypic | ESBL | PFGE,rep-PCR |
| Valverde A. et al. 2008 23 | stool culture | no | genotypic | 99% *E.coli*, 1% *K.pneumoniae* A | genotypic | ESBL | PFGE,multiplex-PCR |
| Lo W.U. et al. 2010 21 | stool culture | no | genotypic | Among all participants:81% *E.coli*, 19% *K. pneumoniae* | genotypic | CTXM | PFGE |
| Tande D. et al. 2010 26 | stool culture | no | genotypic | 56% *E. coli*, unknown proportion of *S.enterica*  | genotypic | ESBL | PFGE |
| Hilty M. et al. 2012 29 | stool culture | no | genotypic | 88% *E.coli,* 12% *K. pneumoniae* | genotypic | ESBL | PFGE,MLST,rep-PCR |
| Löhr I.H. et al. 2013 27 | rectal swab,stool culture | yes | genotypic | 100% *K. pneumoniae* | genotypic | CTXM-15 | PFGE |
| Strenger V. et al. 2013 20 | stool culture | no | genotypic | 44% *K. oxytoca*, 28% *S.marcescens*, 24% *K. pneumoniae*, 4% *E.coli* | phenotypic | ESBL | rep-PCR |
| Adler A. et al. 201418 | rectal swab | no | genotypic | 43% *E.coli*, 27% *K.pneumoniae*, 16% *P.mirabilis,* 6% *Citrobacter spp.*, 5% *Enterobacter spp.*, 3% others | genotypic | ESBL | PFGE,MLST |
| Arcilla MS et al. 2017 24 | stool culture | yes | phenotypic | *Enterobacteriaceae* (no detail) | genotypic | ESBL | N/A |
| Haverkate MR, et al. 2017 28 | stool culture | no | genotypic | 66,7% *E.coli*, 17.9% *K.pneumoniae*, 12.8% *Enterobacter cloacae,* 2.6% *Citrobacter freundii* | genotypic | ESBL | rep-PCR |
| Kurz M.S. et al. 2017 25 | rectal swab | no | phenotypic | 48% *E.coli*, 36% *K.pneumoniae*, 16% *Enterobacter cloacae* B | phenotypic | ESBL | Partial concordance |
| Liakopoulos A. et al. 2018 22 | stool culture | yes | genotypic | 93.7% *E.coli*, 3.75% *Klebsiella pneumoniae,* 2.5% *Enterobacter cloacae* | genotypic | ESBL / AmpC | PFGE,MLST, resistance gene, replicon type and subtype |
| Stewardson AJ et al. 2018 4 | Stool culture | no | Phenotypic  | 100% *E.coli* | phenotypic | ESBL | N/A |

AmpC: AmpC Beta-Lactamase

CTXM: Specific family of genes coding for Extended-Spectrum Beta-Lactamase

CTXM-15: Specific gene coding for Extended-Spectrum Beta-Lactamase

ESBL: Extended-Spectrum Beta-Lactamase

ESBL-PE: Extended-Spectrum Beta-Lactamase Producing Enterobacteriaceae

MLST: MultiLocus Sequence Typing

PCR: Polymerase Chain Reaction

PFGE: Pulsed-field Gel Electrophoresis

Rep-PCR: Repetitive element palindromic Polymerase Chain Reaction

Footnotes to the Supplementary table 1:

A Population based study, pathogens isolated from all study participants

*B Population based study, pathogens isolated from one cohort of the original study (patients recruited at hospital admission)*

Supplementary table 2. Reporting practices of potential biases and confounders in the included studies

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **study design**  | **Study population** | **Sampling criteria** | **Previous hospital stay** | **Antibiotic exposure** | **Travel** | **Foodborne** | **Children in Day care centers** | **Socio-Economic Status** | **Loss to follow up** |
| **baseline** | **follow up**  | **baseline** | **follow up**  | **baseline** | **follow up**  | **baseline** | **follow up**  | **baseline** | **follow up**  | **baseline** |
| Rodriguez-Bano J et al. 2008 19 | cross-sectional study | Index case (Outpatient) | ESBL-PE infection | 19/53A(36%) | na | 38/53B (72%) | na | - | na | 7C  | na | - | na | - | NA |
| Household member | Convenience sample | 6/73A (8%) | na | 8/73B (11%) | na | - | na | 8.55C  | na | - | na | - |
| Valverde A. et al. 2008 23 | cross-sectional study | Index case (Outpatient) | ESBL-PE infection | - | na | 18/36B (50%) | na | - | na | - | na | - | na | - | NA |
| Household member | Convenience sample | - | na | - | na | - | na | - | na | - | na | - |
| Lo W.U. et al. 2010 21 | cross-sectional study | Household members (population based study) | Children with acute respiratory or non-febrile illness | 13/53D (24.5%) | na | 24/53E (45%) | na | - | na | - | na | - | na | - | NA |
| Whole family | 7/172D (4.1%) | na | 40/172E (23%) | na | - | na | - | na | - | na | - |
| Tande D. et al. 2010 26 | longitudinal cohort | Index case (adopted children) | ESBL-PE carriage  | - | - | - | - | - | - | - | - | - | - | - | Not detailed (mean follow time available) |
| Family member | Whole family | - | - | - | - | - | - | - | - | - | - | - |
| Hilty M. et al. 2012 29 | longitudinal cohort | Index case (Inpatient & Outpatient) |  Newly detected ESBL-PE carriage or infection  | 11/82F(13%) | - | 69/82E (84%) | - | - | - | - | - | - | - | - | Not detailed |
| Household member | Convenience sample | - | - | - | - | - | - | - | - | - | - | - |
| Löhr I.H. et al. 2013 27 | longitudinal cohort | Index case (Inpatient, after an outbreak) | ESBL-PE carriage  | naG  | - | 33H (79%) | - | - | - | - | - | - | - | - | Not detailed (median follow time available) |
| Household member | Convenience sample | - | - | - | - | - | - | - | - | - | - | - |
| Strenger V. et al. 2013 20 | longitudinal cohort | Index case (Inpatient) |  ESBL-PE carriage | naG  | 11I (44%)  | 15/25J (60%) | 4/25K (16%) | - | - | - | - | - | - | - | Detailed |
| Household member | Convenience sample | - | - | - | - | - | - | - | - | - | - | - |
| Adler A. et al. 201418 | cross-sectional study | Index case (Inpatient) |  ESBL-PE carriage | 190/194F (98%) | na | 99/194L (51%) | na | - | na | - | na | - | na | - | NA |
| Family member | Convenience sample | 28/286D (9.8%)  | na | 17/286L (6%) | na | - | na | - | na | - | na | - |
| Arcilla MS et al. 2017 24 | longitudinal cohort | Index case (Travellers) M | ESBL-PE carriers | -Q | - | -  | - | - | - | - | - | - | - | - | Not detailed |
| Household member | Convenience sample | - | - | 25/215E (12%) | - | 188/215 (87%) | - | - | - | - | - | 78/215N (36.4%) |
| Haverkate MR, et al. 2017 28 | longitudinal cohort | Index case (Inpatient) | Suspicion of ESBL-PE colonization or infection | 43/74A (58.1%) | - | 53/71O (75%) | 74.6%O (53/71) - 10.5% (4/38) | - | - | - | - | - | - | - | Detailed |
| Household member | Whole family | 4/83A (4.8%) | - | 4/79O (5%) | 5.3%O(4/75) - 1.5% (1/66) | - | - | - | - | - | - | - |
| Kurz M.S. et al. 2017 25 | cross-sectional study | Household members (population based study) | Recruited at hospital admission  | 69/392A (18%) | na | 98/390E (25%) | na | - | na | 221/365P (60.5%) | na | - | na | 117/389N (30.1%) | NA |
| convenience sample | - | na | - | na | - | na | - | na | - | na | - |
| Liakopoulos A. et al. 2018 22 | cross-sectional study | Household members (population based study)Q | Children | - | na | 77/1000R (8%) | na | - | na | 58/1999S (5.7%) | na | 4.6% (95IC: 2.7-6.4) | na | 2.2%T (95IC : 0.6-3.9)  | NA |
| Parents | - | na | 32/1000R (3%) | na | - | na | 675/996U (67.8%) | na | 5.8% (95IC: 3.9-7.8) | na | 4.7%T(95IC : 2.4-7.1) |
| Stewardson AJ et al. 2018 4 | longitudinal cohort | Household members (population based study)Q | With an antibiotic exposure | 33/300D11% | - | 119/300V(40%) | - | 30/300W(10%) | - | 4/300X(1%) | - | 38/300Y(13%) | - | 7/300Z(2%) | Detailed |
| Without antibiotic exposure | 56/416D(13%) | - | 97/416V(23%) | - | 56/416W(13%) | - | 10/416X(2%) | - | 38/300Y(13%) | - | 7/300Z(2%) |
|  |  |  |  |  |  |
| ESBL-PE : Extended-Spectrum Beta-Lactamase Producing Enterobacteriaceae |
| Footnotes to the Supplementary table 2: |
|  |  |  |  |  |  |
| A | Healthcare facility in the last 3 months | J | Cefuroxime/ampicillin exposure during hospital stay | S | Vegetarians in the households |
| B | Antibiotic exposure in the last 2 months  | K  | Antibiotic exposure (without detail) | T | Low SES score |
| C | Av. days of chicken consumption in the previous month  | L | Antibiotic exposure in the last previous month | U | Chicken consumption more than 4 times per month |
| D | Healthcare facility in the last year | M | Data available from the main study population, but not for this nested cohort  | V | Antibiotic exposure in the last year |
| E | Antibiotic exposure in the last 3 months  | N | No education | W | High risk travel reported in the last year |
| F | Referral from another healthcare facility | O | ESBL-selecting antibiotic exposure in the last 3 months (non-including carbapenems) | X | Number of vegetarians |
| G | Neonatal Intensive Care Units admission | P | Eating meat at least once per month | Y | Children <5 years that attend day-care |
| H | Antibiotic exposure during hospital stay | Q | Data not available for the cohort derived in our review, but available for the original cohorts of studies  | Z | Households with only primary education |
| I | Re-hospitalization during follow-up | R | Antibiotic exposure in the last 6 previous months  |  |  |

Supplementary table 3. Potential microbiological biases of the included studies

|  |  |  |  |
| --- | --- | --- | --- |
|  |  | **Potential selection bias** | **Potential detection bias** |
| **Bibliography** | **study design**  | **Colonies analyzed per morphotype** | **Broth use** | **sampling** |
|
| Rodriguez-Bano J et al. 2008 19 | cross-sectional study | >3 colonies and each distinct morphotype | no | not defined |
| Valverde A. et al. 2008 23 | cross-sectional study | 1 colony | no | not defined |
| Lo W.U. et al. 2010 21 | cross-sectional study | <5 colonies | no | not defined |
| Tande D. et al. 2010 26 | longitudinal cohort | 1 colony | no | not defined |
| Hilty M. et al. 2012 29 | longitudinal cohort | not defined | no | not defined |
| Löhr I.H. et al. 2013 27 | longitudinal cohort | 1 colony | yes | self-collected |
| Strenger V. et al. 2013 20 | longitudinal cohort | not defined | no | not defined |
| Adler A. et al. 2014 18 | cross-sectional study | 1 colony | no | not defined |
| Arcilla MS et al. 2017 24 | longitudinal cohort | 1 colony | yes | self-collected |
| Haverkate MR, et al. 2017 28 | longitudinal cohort | 1 colony | no | not defined |
| Kurz M.S. et al. 2017 25 | cross-sectional study | not defined | no | not defined |
| Liakopoulos A. et al. 2018 22 | cross-sectional study | <5 colonies | yes | self-collected |
| Stewardson AJ et al. 2018 4 | longitudinal cohort | 10 colonies | no | self-collected |

Supplementary table 4. Index-case based studies evaluating co-carriage of closely-related and clonally-related ESBL-producing Enterobacteriaceae among household members

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Reference** | **Study period** | **Study design** | **Country** | **Broth use** | **Target pathogen for the index cases** | **Resistance included** | **Type of prevalence**  | **Discrimination**  | **Proportion** | **Co-carriage of**  |
| Rodriguez-Bano J et al. 2008 19 | 2005-2006 | Cross-sectional study | Spain | no | 100% *E. coli* | ESBL | Point prevalence | Closely-related | 27.4% (20/73) | ESBL species  |
| Clonally related | 9.6% (7/73) | ESBL strain  |
| Valverde A. et al. 2008 23 | 2004-2005 | Cross-sectional study | Spain | no | 99% *E.coli*, 1% *K.pneumoniae* | ESBL | Point prevalence | Closely-related | 16.7% (9/54) | ESBL species  |
| Clonally related | 11.1% (6/54) | ESBL strain  |
| Tande D. et al. 2010 26 | 2002-2005 | Prospective cohort study | France | no | 56% *E. coli*, unknown proportion of *S.enterica* | ESBL | Period prevalence (12 months) | Closely-related | 14.3% (7/49) | ESBL-PE |
| Clonally related | 8.16% (4/49) | ESBL strain  |
| Hilty M. et al. 2012 29 | 2008-2009 | Prospective cohort study | Switzerland | no | 88% *E.coli*, 12% *K. pneumoniae* | ESBL | Period prevalence (12 months) | Closely-related | 34.4% (33/96) | ESBL-Ec and ESBL-Kp  |
| Clonally related | 22.9% (22/96) | ESBL strain |
| Löhr I.H. et al. 2013 27 | 2008-2009 | Prospective cohort study | Norway | yes | 100% *K. pneumoniae* | CTXM-15 | Period prevalence (23 months) | Closely-related | 20.0% (12/60) | CTXM-15 species |
| Clonally related | 20% (12/60) | CTXM-15 strain |
| Strenger V. et al. 2013 20 | 2007-2008 | Prospective cohort study | Austria | no | 44% *K. oxytoca*, 28% *S.marcescens*, 24% *K. pneumoniae*, 4% *E.coli* | ESBL | Period prevalence (12 months) | Closely-related | 18.4% (9/49) | ESBL-PE |
| Clonally related | 8.2% (4/49) | ESBL strain  |
| Adler A. et al. 201418 | 2007-2008 | Nested cross-sectional study in a prospective cohort study | France, Italy, Spain, Israel | no | 43% *E.coli*, 27% *K.pneumonia*, 16% *P.mirabilis*, 6% *Citrobacter spp*., 5% *Enterobacter spp*., 3% others | ESBL | Point prevalence  | Closely-related | 8.0% (23/286) | ESBL species  |
| Clonally related | 5.6% (16/286) | ESBL strain  |
| Haverkate M.R. et al. 2017 28 | 2010-2013 | Prospective cohort study | Netherlands | no | 66,7% *E.coli*, 17.9% *K.pneumoniae*, 12.8% *Enterobacter cloacae*, 2.6% *Citrobacter freundii* | ESBL | Period prevalence (18 months)Point prevalence (baseline) | Closely-related | 36.9% (31/84) | ESBL-PE |
| Clonally related | 14.3% (12/84) | ESBL strain  |
| Liakopoulos A. et al. 2018 22 | 2013-2015 | Cross-sectional study | Netherlands | yes | 93.7% *E.coli*, 3.75% *Klebsiella pneumoniae,* 2.5% *Enterobacter cloacae* | ESBL / AmpC | Point prevalence | Closely-related | 18.2% (12/66) | ESBL species sharing the same resistance genes |
| Clonally related | 10,6% (7/66) | ESBL strain |
| Stewardson AJ et al. 2018 4 | 2011-2013 | Prospective cohort study | Belgium, Poland, Switzerland | no | 100% *E.coli* | ESBL | Point prevalence (baseline) | Closely-related | 10.9% (5/46) | ESBL species |

CTXM-15: Specific gene coding for Extended-Spectrum Beta-Lactamase

ESBL: Extended-Spectrum Beta-Lactamase

ESBL Ec: Extended-Spectrum Beta-Lactamase Producing E.coli

ESBL Kp: Extended-Spectrum Beta-Lactamase Producing K.pneumoniae

ESBL-PE: Extended-Spectrum Beta-Lactamase Producing Enterobacteriaceae

Supplementary table 5. Population-based studies evaluating co-carriage level of closely-related and clonally-related ESBL-producing Enterobacteriaceae among multiple families

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  | **Study date** | **Design** | **Country** | **Prevalence type** | **Broth** | **Pathogen included** | **Resistance included** | **Strain relatedness**  | **Proportion** | **co-carriage of**  |
| Lo W.U. et al. 2010 21 | 2007-2008 | Cross-sectional study | China | Point prevalence | no | Among all participants:81% *E.coli*, 19% *K. pneumoniae* | CTXM | Both phenotypic (speciation) and genotypic (susceptibility testing) | 13.6% (83/225) | CTXM-PE |
| Clonally related | 5.8% (13/225) | CTXM strain |
| Kurz M.S. et al. 2017 25 | 2014 | nested cross-sectional study in a prospective cohort study | Rwanda | Point prevalence | no | Index case: 48% *E.coli*, 36% *K.pneumoniae*, 16% *Enterobacter cloacae* | ESBL | closely-related | 15.4% (116/753) | ESBL-PEpartially concordant |

CTXM: Specific family of genes coding for Extended-Spectrum Beta-Lactamase

ESBL: Extended-Spectrum Beta-Lactamase

ESBL-PE: Extended-Spectrum Beta-Lactamase Producing Enterobacteriaceae

Supplementary table 6. Index-case based studies evaluating acquisition rates of closely-related and clonally-related ESBL-producing Enterobacteriaceae among household members

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Author**  | **Study design** | **Country** | **Follow up frequency** | **Follow up time** | **Broth** | **Pathogen included** | **Resistance included** | **Strain relatedness**  | **Acquisition rate (among person-days)** | **Acquisition rate (among person-days at risk)** | **Acquisition of :**  | **Acquisition event**  | **Household members followed** |
| Tande D, et al. 2010 26 | Prospective cohort study | France | 1M | 12 M (median follow up time) | no | *E. coli, Salmonella enterica* *Babelsberg* (56%, unknown proportion of *S.enterica* | ESBL | clonally related | 1.56 acquisitions per 1000 person-weeks | 1.69 acquisitions per 1000 person-weeks at risk | ESBL strain | 4 | 49 |
| Löhr I.H., et al. 2013 27 | Prospective cohort study | Norway | 1M,3M | 23 M (median follow up time for infants and household contacts) | yes | *K.pneumoniae* | CTXM-15 | clonally related | 2.03 acquisitions per 1000 person -weeks | NA | ESBL strain | 12 | 60 |
| Arcilla MS et al. 2017 24 | Prospective cohort study | Netherlands | 1-2W, 1M, 3M, 6M, 12M | 12 | yes | Index case: *Enterobacteriaceae* (no detail) | ESBL | closely-related | 1.50 acquisitions per 1000 person -weeks | NA | ESBL-PE- sharing the same group of resistance gene | 13 | 168 |
| Haverkate MR, et al. 2017 28 | Prospective cohort study | Netherlands | 3M, 6M, 12M, 18M | 18M | no | Gram-negative bacteria (Index case: 67% *E.coli*, 18% *Klebsiella pneumoniae*, 13% *Enterobacter cloacae*) | ESBL | clonally related | 2.01 acquisitions per 1000 person -weeks |  2.90 acquisitions per 1000 person-weeks at risk | ESBL strain | 11 | 71 |
| Stewardson AJ et al. 2018 4 | Prospective cohort study  | Belgium, Poland, Switzerland | Day 8, day 36  | 36.5 (days) | no | 100% *E. coli* | ESBL | closely-related | 17.39 acquisitions per 1000 person -weeks | 19.21 acquisitions per 1000 person-weeks at risk | ESBL species | 5 | 55 |

CTXM-15: Specific gene coding for Extended-Spectrum Beta-Lactamase

ESBL: Extended-Spectrum Beta-Lactamase

ESBL-PE: Extended-Spectrum Beta-Lactamase Producing Enterobacteriaceae

## R code

library(metafor)

library(meta)

library(readxl)

library(ggpubr)

library(ggplot2)

library(boot)

#GENOTYPIC DISCRIMINATION

dat <- read\_excel("O:/UPCI/Romain\_UPCI/Revue systematique household transmission/R\_outcome 13.02\_RM.xlsx", sheet = "cocarriage\_geno2")

#individual estimates with transformation (double-arcsin transformation)

#WHY double-arcsin ? => low proportions, small sample size

ies.da=escalc(xi= case, ni= total, data=dat, measure="PFT", add=0)

#pooled estimates using random effects, with estimation of between-study variance estimator using restricted maximum-likelihood estimator

pes.da=rma(yi, vi, data=ies.da, method="REML")

#conversion to original data

pes=predict(pes.da, transf=transf.ipft.hm, targ=list(ni=dat$total))

print(pes)

#taux-squared, I-squared, and their 95IC, Q-statistic

print(pes.da, digits=4)

confint(pes.da, digits=8)

#forest plot

pes.summary=metaprop(case, total, bibli, data=dat, sm="PFT", method.tau="REML", method.ci="NAsm")

precision=sqrt(ies.da$vi)

forest(pes.summary,

 xlim=c(0,35),

 pscale=100,

 rightcols = FALSE,

 leftcols = c("studlab", "event", "n", "effect", "ci"),

 leftlabs = c("Study", "Cases", "Total", "Proportion (%)", "95% C.I."),

 xlab = "Proportion of co-carriage \namong household members", smlab = "",

 weight.study="random", squaresize=0.5, col.square="navy",

 col.square.lines = "navy",

 col.diamond = "maroon",

 col.diamond.lines = "maroon",

 pooled.totals = FALSE,

 comb.fixed=FALSE,

 fs.hetstat = 10,

 print.tau2=TRUE,

 print.Q=TRUE,

 print.pval.Q=TRUE,

 print.I2=TRUE,

 digits=1,

 sortvar = pubdate)

#Funnel plot avec 95 et 99IC

funnel(pes.da, atransf=transf.ipft.hm, targ=list(ni=dat$total),

 level=c(95, 99), shade=c("white", "gray"))

## Title and Abstract screening form

|  |  |
| --- | --- |
| **Question Text** | **Answer Text** |
| Type of the study:  | Research article (observational, interventional, experimental) |
|   | Review article, recommandation, guideline |
| Does it include Third-Generation Cephalosporin Resistant (3GC-R) Enterobacteriaceae ? | Yes |
|   | No |
|   | Unclear |
| Is it a study of human subjects? (non animal, non in-vitro...) | Yes |
|   | No |
| Are multiple members (including pets) taken from more than one household or family in community? | Yes |
|   | No |
|   | No but case report of one household |
|   | Unclear |
| I still want to include this study in the background material | Yes |
|   | No |

## Full-reading screening form

|  |  |
| --- | --- |
| **Question Text** | **Answer Text** |
| Language barrier (if non-EN indicate the language in comments) | Possible to read |
|   | Impossible to read |
| Type of the study:  | Research article (observational, interventional, experimental) |
|   | Review article, recommendation, guideline |
| Is it a study of human subjects ? (non animal, non in-vitro...) | Yes |
|   | No |
| Does it include 3rd-Generation Cephalosporin Resistant (3GC-R) *E. coli* and/or *K. pneumoniae* ? | Yes |
|   | No |
|   | Unclear |
| Are multiple members (including pets) taken from more than one household or family in community? | Yes |
|   | No |
|   | Unclear |
|   | Yes but case report of a single household |
| Does it only concern: (choose what apply) | Only animal – human transmission but with other animals than pets |
|   | Only animal - human transmission with domestic animals |
|   | Only non-household settings (pig farms, child care facilities, travel, etc…) |
|   | Only mother-to-child transmission (neonatal ≤ 1 month) |
|   | Community outbreak (foodborne...) |
|   | Nothing of the above |
| Does it analyze prevalence, acquisition, co-carriage or transmission rate between household members and/or pets-household members of  3GC-R  *E. coli* and/or *K. pneumoniae*? | Yes |
|   | No |
|   | Unclear |
| Any other comment: |   |

## Plasmidic transfer

Haverkate et al:

* **Method**: PCR-based replicon typing
* **Definition**: different strains sharing the same plasmid incompatibility group and ESBL gene
* **Results**: Among 84 household members at baseline, one shared with an index case the same plasmid incompatibility group and ESBL gene on an unrelated *Klebsiella*. Impossible to determine plasmid acquisition during the follow up because species are not specified in the article.

Liakopoulos et al:

* **Method**: extraction, PCR-based replicon typing, PCR-based replicon sub-typing, PCR-based typing of frequent insertion sequences (ISCR1, ISEcop1, IS26)
* **Definition**: sharing between two different strains of the same ESBL/AmpC gene on the same genetic location on a plasmid belonging to the same replicon type and subtype.
* **Results**: No plasmidic co-carriage between two different strains observed.

Tandé et al:

* **Method**: extraction, electrophoresis
* **Definition**: different strains sharing the same plasmid profile and ESBL gene
* **Results**: no observed plasmid transfer between two different strains observed.