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Epidemic potential of *Escherichia coli* ST131 and *Klebsiella pneumoniae* ST258: a systematic review and meta-analysis

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ABSTRACT

Objectives: Observational studies have suggested that *Escherichia coli* sequence type (ST) 131 and *Klebsiella pneumoniae* ST258 have hyperendemic properties. This would be obvious from continuously high incidence and/or prevalence of carriage or infection with these bacteria in specific patient populations. Hyperendemicity could result from increased transmissibility, longer duration of infectiousness, and/or higher pathogenic potential as compared with other lineages of the same species. The aim of our research is to quantitatively estimate these critical parameters for *E. coli* ST131 and *K. pneumoniae* ST258, in order to investigate whether *E. coli* ST131 and *K. pneumoniae* ST258 are truly hyperendemic clones.

Primary outcome measures: A systematic literature search was performed to assess the evidence of transmissibility, duration of infectiousness, and pathogenicity for *E. coli* ST131 and *K. pneumoniae* ST258. Meta-regression was performed to quantify these characteristics.

Results: The systematic literature search yielded 639 articles, of which 19 data sources provided information on transmissibility (*E. coli* ST131 n=9; *K. pneumoniae* ST258 n=10)), 2 on duration of infectiousness (*E. coli* ST131 n=2), and 324 on pathogenicity (*E. coli* ST131 n=285; *K. pneumoniae* ST258 n=39). Available data on duration of carriage and on transmissibility were insufficient for quantitative assessment. In multivariable meta-regression *E. coli* isolates causing infection were associated with ST131, compared to isolates only causing colonisation, suggesting that *E. coli* ST131 can be considered more pathogenic than non-ST131 isolates. Date of isolation, location and resistance mechanism also influenced the prevalence of ST131. *E. coli* ST131 was 3.2 (95% CI 2.0 to 5.0) times more pathogenic than non-ST131. For *K. pneumoniae* ST258 there were not enough data for meta-regression assessing the influence of colonisation versus infection on ST258 prevalence.

Conclusions: With the currently available data, it cannot be confirmed nor rejected, that *E. coli* ST131 or *K. pneumoniae* ST258 are hyperendemic clones.

Strengths and limitations of this study

- A comprehensive literature search combined with meta-regression analyses was performed to quantify evidence of hyperendemicity of *Escherichia coli* ST131 and *Klebsiella pneumoniae* ST258 focusing on transmissibility, durations of infectiousness and pathogenicity.
- There is a large heterogeneity in reported prevalences and a limited amount of data available on transmissibility and duration of infectiousness.
- With the currently available data, it can neither be confirmed nor rejected, that *E. coli* ST131 or *K. pneumoniae* ST258 are hyperendemic clones.

INTRODUCTION

Infections caused by *Escherichia coli* and *Klebsiella pneumoniae* producing extended-spectrum β-lactamases (ESBL) or carbapenemases, are increasing worldwide. There is growing evidence that certain clonal lineages of these species, such as *E. coli* sequence type (ST) 131 and *K. pneumoniae* ST258, have more epidemic potential than other lineages within their species group. *E. coli* ST131 was first described in 2008[1] and *K. pneumoniae* ST258 in 2009.[2] *E. coli* ST131 is reported from around the globe, both in healthcare settings and in the community,[3 4] and is mostly associated with ESBL production and fluoroquinolone resistance.[3 5] *K. pneumoniae* ST258 is mainly associated with *K. pneumoniae* carbapenemase (KPC) production, and other resistance mechanisms,[6] and is widespread in the USA, and expanding in Europe.[6–8] In the scientific literature, *E. coli* ST131 and *K. pneumoniae* ST258 are widely considered hyperendemic clones.[3 5 6 8 9] But the evidence underlying these assumptions is not that obvious.[3 5] If *E. coli* ST131 or *K. pneumoniae* ST258 are truly hyperendemic clones, interventions may be targeted to these specific clones.

From a simple model in which patients can be susceptible, colonised or infected (figure 1), the characteristics of hyperendemicity follow as explained below. Susceptible hosts can acquire colonisation through

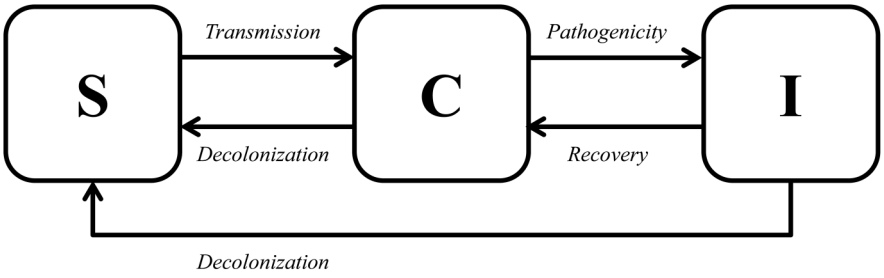

Figure 1 Simple model.

transmission, either directly (from another colonised or infected person) or indirectly (from the environment or via the hands of healthcare workers). Both colonised and infected patients contribute to transmission, as long as they are infectious, which can be expressed with the duration of colonisation. Duration of colonisation can be influenced by fitness cost associated with resistance or by antibiotic use. Colonisation can proceed to infection, which typically occurs in a fraction of colonised patients,[10] and the rate of this progression can be expressed as the pathogenicity level. Decolonisation can occur in both colonised and infected persons.

To be hyperendemic, a clone has to have advantages over other clones in at least one of the traits: transmissibility, duration of colonisation or pathogenicity. Therefore, we define a hyperendemic clone as 'a clone that is more transmissible, has a longer duration of colonisation, and/or is more pathogenic than other clones of the same species'. The presence of any or more of these traits will then lead to a continuously high incidence and/or prevalence of carriage or disease in a specific patient population. We performed a systematic review to quantitatively estimate these critical parameters for *E. coli* ST131 and *K. pneumoniae* ST258, in order to investigate whether *E. coli* ST131 and *K. pneumoniae* ST258 are truly hyperendemic clones.

METHODS

Search strategy

A PubMed and EMBASE search was performed to retrieve relevant articles published until 1 January 2015. The complete search string can be found in online supplementary text 1. A cross-reference check was performed to include relevant articles not found during the search. Only English, full-text articles were included. Articles unavailable online were requested from the authors. The Meta-analysis Of Observational Studies in Epidemiology statement[11] was followed for reporting in this paper.

Study selection

Titles and abstracts were independently reviewed by two reviewers (MRH and MJDD) and selected for further review if they met the inclusion criteria. Selections were compared between the two reviewers, and if consensus was not reached, a third reviewer (MCJB or MJMB) was consulted.

The inclusion criteria for articles on transmissibility were that possible transmissions should be described, and the number of cases should be reported. Outbreak reports were included. Articles focusing on duration of colonisation should include at least two cultures per patient taken at two different time points. Pathogenicity was defined as the difference in the prevalence of ST131 or ST258 in infections (clinical isolates) compared to colonisation. We considered a clone to be more pathogenic when the relative abundance of this clone in isolates causing infections is higher compared to isolates associated with colonisation. Therefore, articles on pathogenicity of *E. coli* ST131 or *K. pneumoniae* ST258 should report the prevalence or incidence of infections among patients colonised with *E. coli* ST131 or *K. pneumoniae* ST258, the prevalence of *E. coli* ST131 or *K. pneumoniae* ST258 among patients colonised with *E. coli* or *K. pneumoniae*, respectively, or the prevalence of *E. coli* ST131 or *K. pneumoniae* ST258 among at least 10 clinical isolates of *E. coli* or *K. pneumoniae*, respectively.

Articles were excluded if they did not contain original data (such as reviews, commentaries, or articles reusing existing data sets), if they considered *E. coli* or *K. pneumoniae* only in non-human sources, or if there was no clear information on the isolate collection or selection.

Data extraction

Data were extracted by the same two reviewers independently, and crosschecked using a standard form developed by the researchers. Data were collected on population and setting, recording if participants were inpatients, outpatients/community residents, travellers or from another/unknown group. The area/region where the study took place was recorded and categorised into (mainly) from Africa, Asia, Australia, Europe, North America and South America. It was recorded whether data collection took place during an outbreak period, and if a selection on antibiotic susceptibility or resistance was made, divided into selection on ESBL/AmpC-producing isolates (including third-generation cephalosporin-resistant isolates), carbapenem-resistant or carbapenemase-producing Enterobacteriaceae (CRE/CPE, eg, KPC, OXA-48), other resistance profiles (eg, ciprofloxacin-resistant, fluoroquinolone-susceptible or multidrug resistant), or no selection on resistance. Furthermore, the method to detect sequence types was documented, split up into multilocus sequence typing

(MLST, when all isolates were typed by MLST), extrapolation based on pulsed-field gel electrophoresis (PFGE, when only selected isolates were typed with MLST and the sequence types were inferred based on PFGE type), (PCR, when all isolated underwent PCR-screening for ST-specific alleles), extrapolation based on PCR (mainly MLST for *E. coli* isolates that were positive for O25b-ST131 by PCR), or other/unknown (such as fumC/fimH typing). Also, the sample site of the included isolates (percentage of isolates isolated from blood, urine, gastrointestinal, respiratory, wound/abscess or other sites), and time period of the study were recorded. For the time period, the middle date was used in the model if the study covered a longer time period.

For transmissibility, if available, information was gathered on admission prevalence, number of cases, number of uncolonised patients and transmission measure given. For duration of colonisation, the number of cases and duration of colonisation was recorded. For pathogenicity, information was collected on the prevalence or incidence of infections in patients colonised with *E. coli* ST131 or *K. pneumoniae* ST258, the prevalence of *E. coli* ST131 or *K. pneumoniae* ST258 in patients colonised with *E. coli* or *K. pneumoniae*, respectively, and/or the prevalence of *E. coli* ST131 or *K. pneumoniae* ST258 in patients infected with *E. coli* or *K. pneumoniae*, respectively.

Quality of the included articles was assured by only including papers with a proper selection of isolates. Furthermore, quality was implicitly incorporated in the data that were collected on the detection method used, the sample sites, whether data were collected during an outbreak and the setting and time period in which data were collected.

Several studies allowed splitting the data into multiple 'data sources'. For example, if data was available per year or per country, these were recorded separately. Figure 2 shows a flow diagram with the included and excluded articles. Since only 19 data sources were available on transmissibility (9 on *E. coli* ST131 and10 on *K. pneumoniae* ST258), and two on duration of colonisation (both on *E. coli* ST131), we could only describe these without quantifying summary measures. For pathogenicity, enough data was available on *E. coli* to do a meta-regression analysis and calculate summary measures.

Meta-regression pathogenicity

In order to evaluate the pathogenicity of *E. coli* ST131 and *K. pneumoniae* ST258, and to assess which factors influence this, meta-regression was performed using all reported data on the prevalence of *E. coli* ST131 in clinical (infection) or screening (colonisation) isolates of *E. coli*, and for all reported data on the prevalence of *K. pneumoniae* ST258 in clinical (infection) isolates of *K. pneumoniae*. The prevalence estimates (calculated as the number of ST131-positive or ST258-positive isolates divided by the total number of *E. coli* or *K. pneumoniae* isolates, respectively) and standard errors (SEs) were logit transformed in the analysis. Heterogeneity between studies was evaluated with Cochrans's Q and the I^2 statistic.[12] Because of high heterogeneity (I^2 >75%), a meta-analysis using a generalised linear

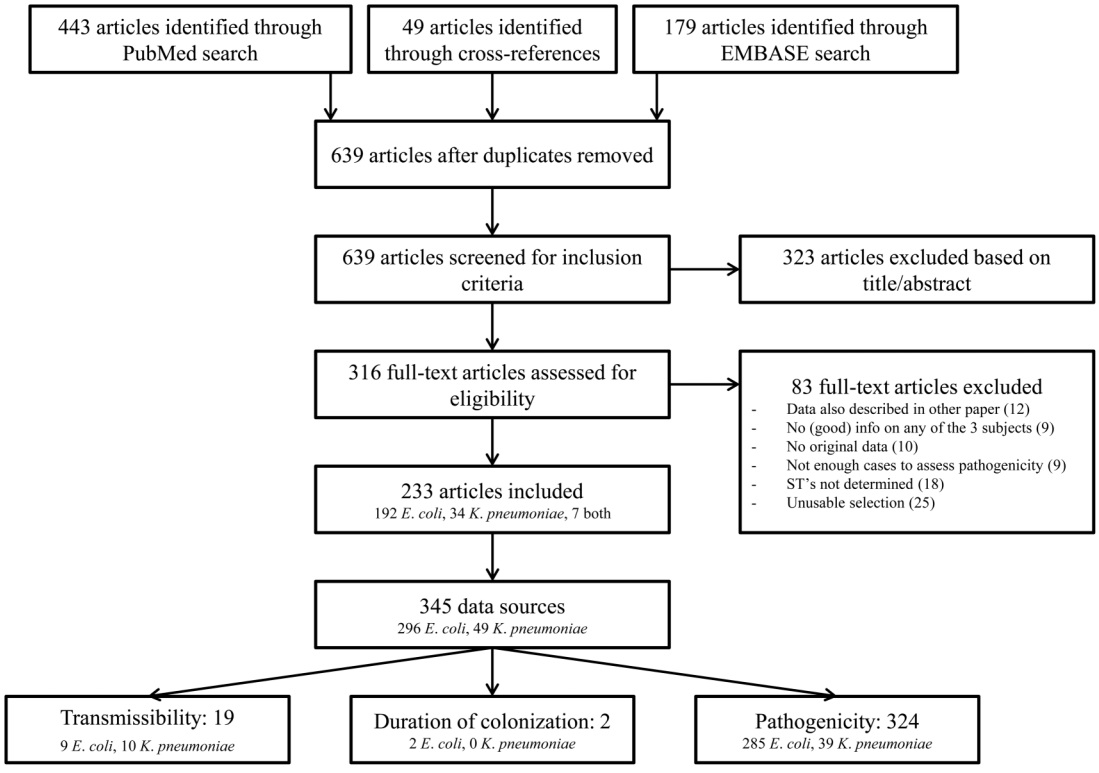

Figure 2 Flow chart of article selection.

mixed-effect model with random effects per data source was used to assess sources of variability in the overall prevalence estimates. Univariate analyses were performed to identify covariates associated with the overall prevalence estimates. All covariates with a p value <0.20 were included in the multivariate model, and backward selection was performed using the likelihood ratio test. There, as we are performing an exploratory analysis, a cut-off of p<0.10 was used to determine statistical significance. The variable describing sample site was not included in the models, because of great dependency on the type of isolate (clinical or screening isolate, eg, blood isolates representing infection), and the effect of culture site, might not be comparable for isolates representing colonisation or infection. The estimated between-study variance (τ^2) was evaluated for the model with and without explanatory parameters. The exponent of the coefficient for colonisation/infection found in the metaregression model is an OR, which can be interpreted as a risk ratio. This was taken as a measure of how much more pathogenic *E. coli* ST131 was compared to non-ST131, that is, a value of 2 would indicate that per colonised day colonisation with ST131 leads two times more often to an infection as compared to colonisation with non-ST131. All analyses were performed in R V.3.0.3 (http://CRAN.R-project.org) using the 'metafor' package.

RESULTS

In all, 345 useful data sources were identified (see figure 2 for the consecutive steps followed for identification). For transmissibility, 19 data sources were identified; for duration of carriage, 2; and for pathogenicity, 324. Most studies (n=206, 72%) were performed in Europe and North America, and 266 (93%) were performed in a non-outbreak setting (table 1). *E. coli* isolates were most selected on ESBL production or resistance against third-generation cephalosporins, and *K. pneumoniae* isolates on being CRE/CPE. Colonisation isolates were most often from gastrointestinal origin (85.2%), and infection isolates from urine (54.8%) or blood (24.5%).

Transmissibility

There were 19 studies reporting transmissibility of *E. coli* ST131 (n=9) and *K. pneumoniae* ST258 (n=10), some being case reports or describing single possible transmission events (table 2). Transmission events for *E. coli* ST131 have been described or suggested in household (n=4), day care (n=1), nursing home (n=1) and hospital settings (n=4). For *K. pneumoniae* ST258 all sources reported on transmission events in hospital settings, and all included CRE/CPE.

Transmissibility can be quantified by the number of transmissions per patient, or patient-days at risk, which requires information on the number of index cases, number of transmissions, and number of days or patients at risk. Yet, one or more of these aspects, especially time at risk, is missing in all studies but one. Most studies are cross-sectional studies, in which transmission cannot be proven.

Differences in transmission capacity between *E. coli* ST131 and non-ST131, or between *K. pneumoniae* ST258 and non-ST258, have not been quantified, precluding any conclusion on the relative transmissibility of *E. coli* ST131 and *K. pneumoniae* ST258 compared to other clonal lineages.

Duration of carriage

The duration of carriage of *E. coli* ST131 was investigated in two studies. In one study, colonisation with *E. coli* was still apparent after 12 months in 64% (n=9), and 40% (n=14) of those carrying *E. coli* ST131 or other STs, respectively (p=0.12).[32] In another study, of two patients acquiring colonisation with *E. coli* ST131 during travel, one was a prolonged carrier with this strain. However, the definition of prolonged carriage was not given.[33] The duration of carriage of *K. pneumoniae* ST258 has not been determined.

Pathogenicity

E. coli

From 285 data sources, we retrieved data from 34 253 *E. coli* isolates (2041 associated with colonisation and 32 212 with infection). Prevalence of *E. coli* ST131 in these studies ranged from 0% to 100% (see online supplementary figure S1), with high statistical heterogeneity between studies (I^2=96.9%).

In univariable meta-regression the *E. coli* ST131 prevalence in individual studies increased in time, and appeared to be influenced by whether isolates were associated with infection or colonisation, resistance patterns used for isolate selection and location, where the study was performed (p value <0.20; table 3). These variables were included in the multivariable meta-regression model, and time, location and selection remained significantly associated with *E. coli* ST131 prevalence (table 4). No significant effects were present for study population, microbiological methods used to detect ST131, or whether the study was performed in an outbreak situation or not.

The prevalence of ST131 was highest if *E. coli* isolates were selected upon the presence of ESBL production, or third-generation cephalosporin resistance, and lowest if derived from non-selective media. Prevalence of *E. coli* ST131 was highest in North America, and lowest in South America. The estimated prevalence of ST131 in *E. coli*, given particular values of the covariates, can be derived from the regression equation (table 4). For example, the estimated logit (prevalence ST131) for isolates causing infection, selected on presence of ESBL, in North America in January 2010 is given by 2.9668 +12×0.0140+1.1545+1.3826+0.4436=0.1819, which corresponds to a prevalence of ST131 of exp(0.1819)/(1+exp (0.1819))=54.5%. The estimated prevalence in the

Table 1 Characteristics of included studies

	EC transmissibility (n=9)	KP transmissibility (n=10)	EC duration (n=2)	EC pathogenicity colonisation (n=35)	EC pathogenicity infection (n=249)	KP pathogenicity colonisation (n=3)	KP pathogenicity infection (n=35)	KP pathogenicity colonisation and infection (n=1)
Number of isolates (mean, SD)				58 (67)	129 (357)	59 (69)	40 (64)	
Number of isolates (median, IQR)				36 (21–62)	53 (20–115)	36 (20–87)	20 (14–41)	
Population—inpatients	2 (22.2%)	8 (80.0%)	1 (50.0%)	11 (31.4%)	128 (51.4%)	3 (100.0%)	24 (68.6%)	0 (0.0%)
Population—outpatients/ community	6 (66.7%)	2 (20.0%)	0 (0.0%)	18 (51.4%)	25 (10.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Population—mixed	1 (11.1%)	0 (0.0%)	0 (0.0%)	2 (5.7%)	63 (25.3%)	0 (0.0%)	2 (5.7%)	1 (100.0%)
Population—travellers	0 (0.0%)	0 (0.0%)	1 (50.0%)	3 (8.6%)	3 (1.2%)	0 (0.0%)	1 (2.9%)	0 (0.0%)
Population—other/unknown	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	30 (12.0%)	0 (0.0%)	9 (25.7%)	0 (0.0%)
Continent—Africa	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (5.7%)	16 (6.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Continent—Asia	2 (22.2%)	0 (0.0%)	0 (0.0%)	9 (25.7%)	42 (16.9%)	0 (0.0%)	4 (11.4%)	0 (0.0%)
Continent—Australia	0 (0.0%)	0 (0.0%)	1 (50.0%)	3 (8.6%)	10 (4.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Continent—Europe	4 (44.4%)	7 (70.0%)	1 (50.0%)	14 (40.0%)	96 (38.6%)	2 (66.7%)	14 (40.0%)	0 (0.0%)
Continent—North America	3 (33.3%)	1 (10.0%)	0 (0.0%)	7 (20.0%)	79 (31.7%)	1 (33.3%)	11 (31.4%)	1 (100.0%)
Continent—South America	0 (0.0%)	2 (20.0%)	0 (0.0%)	0 (0.0%)	6 (2.4%)	0 (0.0%)	6 (17.1%)	0 (0.0%)
Outbreak setting	3 (33.3%)	10 (100.0%)	0 (0.0%)	1 (2.9%)	4 (1.6%)	1 (33.3%)	8 (22.9%)	0 (0.0%)
Selection—ESBL/3GC-R	8 (88.9%)	0 (0.0%)	1 (50.0%)	23 (65.7%)	182 (73.1%)	2 (66.7%)	0 (0.0%)	0 (0.0%)
Selection—CRE/CPE	0 (0.0%)	9 (90.0%)	0 (0.0%)	0 (0.0%)	8 (3.2%)	1 (33.3%)	29 (82.9%)	1 (100.0%)
Selection—other	1 (11.1%)	0 (0.0%)	1 (50.0%)	5 (14.3%)	31 (12.4%)	0 (0.0%)	5 (14.3%)	0 (0.0%)
Selection—none	0 (0.0%)	1 (10.0%)	0 (0.0%)	7 (20.0%)	28 (11.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Detection—MLST	6 (66.7%)	4 (40.0%)	0 (0.0%)	10 (28.6%)	134 (53.8%)	1 (33.3%)	25 (71.4%)	0 (0.0%)
Detection—extrapolation based on PFGE	1 (11.1%)	3 (30.0%)	0 (0.0%)	3 (8.6%)	15 (6.0%)	1 (33.3%)	9 (25.7%)	1 (100.0%)
Detection—extrapolation based on PCR	2 (22.2%)	0 (0.0%)	2 (100.0%)	21 (60.0%)	83 (33.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Detection—CH	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	13 (5.2%)	1 (33.3%)	0 (0.0%)	0 (0.0%)
Detection—other/unknown	0 (0.0%)	2 (20.0%)	0 (0.0%)	1 (2.9%)	4 (1.6%)	0 (0.0%)	1 (2.9%)	0 (0.0%)
Site—blood	1 (11.1%)	3 (30.0%)	0 (0.0%)	0 (0.0%)	64 (25.7%)	0 (0.0%)	7 (20.0%)	0 (0.0%)
Site—urine	2 (22.2%)	3 (30.0%)	1 (50.0%)	2 (5.7%)	143 (57.4%)	1 (33.3%)	12 (34.3%)	1 (100.0%)
Site—gastrointestinal tract	6 (66.7%)	3 (30.0%)	1 (50.0%)	32 (91.4%)	5 (2.0%)	1 (33.3%)	7 (20.0%)	0 (0.0%)
Site—respiratory tract	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.9%)	3 (1.2%)	1 (33.3%)	3 (8.6%)	0 (0.0%)
Site—wound	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Site—other/unknown	0 (0.0%)	1 (10.0%)	0 (0.0%)	0 (0.0%)	33 (13.3%)	0 (0.0%)	6 (17.1%)	0 (0.0%)

CH, fumC/fimH typing; CPE, carbapenemase-producing Enterobacteriaceae; CRE, carbapenem-resistant Enterobacteriaceae; EC, *Escherichia coli*; ESBL, extended-spectrum beta-lactamase; KP, *Klebsiella pneumoniae*; KPC, *Klebsiella pneumoniae* carbapenemase; MLST, multilocus sequence typing; PFGE, pulsed-field gel electrophoresis; Site, site from which most isolates were identified.

Table 2 Summary of articles describing transmissibility of *Escherichia coli* ST131 and *Klebsiella pneumoniae* ST258

Author (year)	Country	Year	Setting	Organism	Resistance mechanism	Index cases (n)	Secondary cases (n)	Uncolonised	Exposure time
Veenemans (2014)[13]	The Netherlands	2013	Nursing homes	*E. coli* ST131	ESBL	5 and 3			
Kojima (2014)[14]	Japan	2009–2010	Household	*E. coli* ST131	ESBL	1	2		
Blanc (2014)[15]	France	2012	Day care centers	*E. coli* ST131	ESBL	7			
Giuffrè (2013)[16]	Italy	2012	Neonatal intensive care unit	*E. coli* ST131	ESBL	15		88	
Adler (2012)[17]	Israel	2008–2009	Geriatric rehabilitation wards	*E. coli* ST131	ESBL	21	23	367	
				E. coli non-ST131	ESBL	31	36	367	
Hilty (2012)[18]	Switzerland	2008–2010	University hospital	*E. coli* ST131	ESBL	13	2	36	48 index inpatients for a total of 400 000 patient-days
				E. coli non-ST131	ESBL	27	2	48	
			Household	*E. coli* ST131	ESBL	15	7	19	
				E. coli non-ST131	ESBL	42	13	49	
Owens (2011)[19]	USA	Before 2011	Household	*E. coli* ST131	ESBL	2			
Johnson (2010)[20]	USA	Before 2010	Household	*E. coli* ST131	Fluoro-quinolone resistance	1	1	1	
Ender (2009)[21]	USA	Before 2009	Hospital	*E. coli* ST131	ESBL	1	1		
Marquez (2014)[22]	Uruguay	2011	Intensive care unit	*K. pneumoniae* ST258	KPC	1	1	3	
Garza-Ramos (2014)[23]	Mexico	2012–2013	2 Hospitals	*K. pneumoniae* ST258	KPC	15 and 3			
Gaibani (2014)[24]	Italy	2010	Hospital	*K. pneumoniae* ST258	KPC	11			
Giuffrè (2013)[25]	Italy	2012	Neonatal intensive care unit	*K. pneumoniae* ST258	KPC	10		44	
Tofteland (2013)[26]	Norway	2010	Intensive care unit	*K. pneumoniae* ST258	KPC	6			
Morris (2012)[27]	Ireland	2011	2 Hospitals	*K. pneumoniae* ST258	KPC	11			
Agodi (2011)[28]	Italy	2009	Hospital	*K. pneumoniae* ST258	KPC	16			
Won (2011)[29]	USA	2008	Acute care hospitals and long-term acute care hospitals	*K. pneumoniae* ST258	KPC	33 (+7 presumed cases)			
Marchese (2010)[30]	Italy	2009	Neuro-rehabilitation unit	*K. pneumoniae* ST258	KPC	4 (+3 at time of publication)			
Mammina (2010)[31]	Italy	2009	Intensive care unit	*K. pneumoniae* ST258	KPC	13			

Table 3 Effect of covariates on prevalence of ST131 in *Escherichia coli* (univariable random effects meta-regression models)

	p Value
Study period (per month*)	0.0011
Infection or colonisation	0.0002
Colonisation	
Infection	
Outbreak setting	0.9112
Selection of isolates based on resistance pattern	<0.0001
No selection on resistance profile	
ESBL/3GC-R	
CRE/CPE	
Other	
Study population	0.6219
Inpatients	
Outpatients/community	
Mixed	
Travellers	
Other/unknown	
Location	<0.0001
Europe	
North America	
South America	
Australia	
Asia	
Africa	
Method used to detect ST131	0.3598
MLST	
Extrapolation based on PFGE	
PCR	
Extrapolation based on PCR	
Other/unknown	

*Reference date: 1 January 2009.
CRE/CPE, carbapenem-resistant Enterobacteriaceae/carbapenemase-producing Enterobacteriaceae; ESBL/3GC-R, extended-spectrum β-lactamases/third-generation cephalosporin resistance; MLST, multi-locus sequence typing; PFGE. pulsed-field gel electrophoresis.

Table 4 Effect of covariates on prevalence of ST131 in *Escherichia coli* (multivariable random effects meta-regression model)

	Estimate (SE*)	p Value
Intercept	−2.9668 (0.2959)	
Study period (per month†)	0.0140 (0.0023)	<0.0001
Infection or colonisation		<0.0001
Colonisation	Reference	
Infection	1.1545 (0.2281)	
Selection of isolates based on resistance pattern		<0.0001
No selection on resistance profile	Reference	
ESBL/3GC-R	1.3826 (0.2207)	
CRE/CPE	0.5994 (0.4879)	
Other	0.9058 (0.2709)	
Location		<0.0001
Europe	Reference	
North America	0.4436 (0.1675)	
South America	−2.2868 (0.6101)	
Australia	−0.4209 (0.3407)	
Asia	−0.3657 (0.1927)	
Africa	−0.2246 (0.3154)	

*Parameter estimates (SEs) are presented on a logit scale.
†Reference date: 1 January 2009.
CRE/CPE, carbapenem-resistant Enterobacteriaceae/carbapenemase-producing Enterobacteriaceae; ESBL/3GC-R, extended-spectrum β-lactamases/third-generation cephalosporin resistance.

reference category (January 2009, colonisation, no selection on resistant profile, Europe) is exp(−2.9668)/(1+exp(−2.9668))=4.9%.

In the multivariable meta-regression model, *E. coli* ST131 was significantly associated with infection compared to colonisation, suggesting that ST131 isolates are more pathogenic than non-ST131 isolates. From the infection/colonisation coefficient, we can calculate the relative pathogenicity of *E. coli* ST131 compared to non-ST131. We found that *E. coli* ST131 is 3.2 (95% CI 2.0 to 5.0) times more pathogenic than non-ST131. Online supplementary figure S2 shows the proportion of ST131 found in infection isolates compared to colonisation isolates as estimated by the meta-regression model.

The estimated between-study variance (τ^2) reduced from 1.68 in the model without parameters to 1.1 in the final model, implying that a high level of heterogeneity remained.

K. pneumoniae

There were 35 and three data sources providing information on the prevalence of ST258 *K. pneumoniae* in clinical and colonising isolates, respectively (see online supplementary figure S3). Because of limited data on colonisation, quantitative analyses were performed for clinical isolates only.

In the univariable meta-regression model, outbreak setting yes/no, selection of isolates based on resistance pattern, study population and geographic location were all associated with a higher prevalence of ST258 with a p value <0.20 and were, thus, included in the multivariable model (table 5). If data were collected during an outbreak of *K. pneumoniae*, this was associated with a higher prevalence of ST258 (table 6). Furthermore, the model yielded a significant effect of resistance patterns on the prevalence of ST258 in *K. pneumoniae*. ST258 prevalence was associated with selection of isolates on CRE-positivity, but the number of data sources describing isolates that are not CRE/CPE is low and varied (n=5). Furthermore, study population characteristics also appeared to influence ST258 prevalence in *K. pneumoniae*, with higher prevalence of ST258 in inpatients, compared to 'other' populations. Yet, the 'other' group is not defined accurately, precluding firm conclusions. Only one data source was available for outpatients or persons residing in the community. Finally, the reported ST258 prevalence was lower in Asia and Australia than in other continents.

Table 5 Effect of covariates on prevalence of ST258 in clinical isolates of *Klebsiella pneumoniae* (univariable random effects meta-regression models)

	p Value
Study period (per month*)	0.6109
Outbreak setting	0.0052
Selection of isolates based on resistance pattern	0.0543
Non-CRE/CPE	
CRE/CPE	
Study population	0.0265
Inpatients	
Mixed	
Other/unknown	
Location	0.1013
Europe	
North America	
South America	
Asia (including Australia)	
Method used to detect ST258	0.2253
MLST	
Extrapolation based on PFGE	

*Reference date: 1 January 2009.
CRE/CPE, carbapenem-resistant Enterobacteriaceae/carbapenemase-producing Enterobacteriaceae; MLST, multi-locus sequence typing; PFGE, pulsed-field gel electrophoresis.

The estimated prevalence of ST258 in *K. pneumoniae*, given particular values of the covariates, can be derived from the regression equation. For example, the estimated logit (prevalence of ST258) for isolates selected on presence of CRE in hospital inpatients in North America during an outbreak is given by −0.0.0320 +2.8038+0.3332=3.1050, which corresponds to a prevalence of ST258 of exp(3.1050)/(1+exp(3.1050)=95.7%. The estimated prevalence in the reference category (during an outbreak, non CRE/CPE, hospital inpatients, Europe) is exp(−0.0320)/(1+exp(−0.0320))=50.8%.

Table 6 Effect of covariates on prevalence of ST258 in clinical isolates of *Klebsiella pneumoniae* (multivariable random effects meta-regression model)

	Estimate (SE*)	p Value
Intercept	−0.0320 (1.0008)	0.9745
Outbreak setting		<0.05
Yes	Reference	
No	−1.7725 (0.7833)	
Selection of isolates based on resistance pattern		<0.01
Non-CRE/CPE	Reference	
CRE/CPE	2.8038 (0.9445)	
Study population		<0.01
Inpatients	Reference	
Mixed	−3.8232 (1.5480)	
Other/unknown	−2.2908 (0.7255)	
Location		<0.05
Europe	Reference	
North America	0.3332 (0.7607)	
South America	0.4213 (0.9038)	
Asia (including Australia)	−2.0716 (0.7833)	

*Parameter estimates (SEs) are presented on a logit scale.
CRE/CPE, carbapenem-resistant Enterobacteriaceae/carbapenemase-producing Enterobacteriaceae.

The estimated between-study variance (τ^2) reduced from 6.43 in the model without parameters to 2.25 in the final model, indicating a considerable improvement, but still a high level of heterogeneity.

ST258 was not detected in two studies reporting on colonisation with *K. pneumoniae*, that included 36 and 4 isolates, respectively.[184 219] Only from the study of van Duin *et al*[224] can we deduce a prevalence of ST258 in *K. pneumoniae* of 31% in colonising isolates. This precludes any quantification of the pathogenicity of *K. pneumoniae* ST258.

The only study in which both colonisation and infection with *K. pneumoniae* ST258 were investigated included a set of seven KPC-producing *K. pneumoniae* ST258 isolates collected from a long-term acute-care facility in South Florida.[245] Three patients were colonised, and four had both colonisation and infection. Again, the sample size is too small for drawing conclusions.

DISCUSSION

Based on published information, we conclude that there is evidence that *E. coli* ST131 is more pathogenic than *E. coli* non-ST131, but not for increased transmissibility or prolonged duration of carriage. Because of the heterogeneity in the data, it cannot be concluded (nor rejected) that *E. coli* ST131 is a hyperendemic clone. For *K. pneumoniae* ST258, the published data precluded any conclusion on increased transmissibility, longer duration of carriage or increased pathogenicity.

Several limitations in our study should be acknowledged. Because of our search strategy, the prevalence of *E. coli* ST131 and *K. pneumoniae* ST258 that were retrieved are likely overestimations of the real prevalence. We required the articles to report ST131/ST258 in their title and/or abstract, and therefore, articles that did not report this, or that did not detect ST131/ST258 in their study, may have been missed. Since the prevalence is dependent on factors including time, location, resistance pattern, population studied and possibly variables not included in this review (eg, patient-specific details like age, gender), we deemed it not meaningful to estimate an overall prevalence of ST131 in *E. coli* or ST258 in *K. pneumoniae*.

We also did not create a funnel plot to assess publication bias, as such an analysis also assumes that there is one overall effect or prevalence. Thus, publication bias cannot be excluded. It is possible that identification of *E. coli* ST131 or *K. pneumoniae* ST258 stimulates publication because of the current interest in these clones. However, this will most likely equally influence studies reporting infection and colonisation isolates, which

would not influence our conclusions. Also, the finding of ESBL or KPC might instigate investigation of sequence types. As 70% of the included studies on *E. coli* selected isolates based on the presence of ESBL or 3GC-R, our findings might be more applicable to ESBL-producing *E. coli* ST131 than all *E. coli* ST131 in general. The same holds for *K. pneumoniae*, for which around 90% of included studies selected isolates based on the presence of carbapenemase production of carbapenem resistance, mainly corresponding to KPC production. In our analysis, we used grouped variables (eg, continent instead of country), as there are limitations to the number of variables that can be studied.

There could also be differences in detecting infection and colonisation-associated isolates. Infection isolates are mainly collected retrospectively, when a pattern or outbreak is recognised, whereas, colonisation isolates are more often collected prospectively. Yet, since determination of sequence types is unambiguous, it is unlikely that such differences have affected our conclusions.

Our analysis clearly demonstrates that more—and better designed—studies are needed to determine whether *E. coli* ST131 and *K. pneumoniae* ST258 are truly hyperendemic clones. This would be possible with a prospective cohort study of a population (eg, the general population or hospitalised patients) with a certain contact structure, in which carriage with *E. coli* or *K. pneumoniae* is regularly (eg, weekly or monthly) determined. As *K. pneumoniae* ST258 is mainly a healthcare-associated pathogen, choice of study population might be different than for *E. coli* ST131, that is also a community-associated pathogen. For determination of transmissibility, genotyping should be performed, preferably with highly discriminatory methods, and preferably with inclusion of multiple isolates per patient.[246] The duration of exposure to persons colonised or infected with *E. coli* ST131/*K. pneumoniae* ST258 should be determined to calculate the number of acquisitions per unit of time. Carriers could be studied in more detail to determine the duration of carriage and the infection rate (and duration until infection), preferably with inclusion of the effects of antibiotic use on these parameters. There should be a sufficient duration of follow-up, and isolates should be characterised to determine whether multiple isolates represent persistent carriage or recolonisation with different strains.

In conclusion, current evidence does not allow the conclusion that *E. coli* ST131 and *K. pneumoniae* ST258 are hyperendemic clones.

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