

Transmission routes of ESBL/pAmpC producing bacteria in the broiler production pyramid, a literature review



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ABSTRACT

Plasmid mediated Extended Spectrum Beta-Lactamase and AmpC Beta-Lactamase (ESBL/pAmpC) producing bacteria are resistant to beta-lactam antimicrobials and are widespread in humans, the environment and animals. Animals, especially broilers, are an important reservoir of ESBL/pAmpC producing bacteria. To control ESBL/pAmpC prevalence in broilers, transmission within the entire broiler production pyramid should be considered. This study, including 103 articles originating from two electronic databases, searched for evidence for possible routes of transmission of ESBL/pAmpC producing bacteria in the broiler production pyramid. Possible routes of transmission were categorised as 1) vertical between generations, 2) at hatcheries, 3) horizontal on farm, and 4) horizontal between farms and via the environment of farms. This review presents indications for transmission of ESBL/pAmpC producing bacteria for each of these routes. However, the lack of quantitative results in the literature did not allow an estimation of the relative contribution or magnitude of the different routes. Future research should be specifically targeted towards such information as it is crucial to guide reduction strategies for the spread of ESBL/pAmpC producing bacteria in the broiler production chain.

1. Introduction

Antimicrobial resistance (AMR) is an increasing threat to human health (World Health Organization, 2016). An important group of antimicrobial resistant bacteria is associated with plasmid mediated Extended Spectrum Beta-Lactamase and AmpC Beta-Lactamase (ESBL/pAmpC) producing bacteria. These beta-lactamase producing bacteria hydrolyse beta-lactam antimicrobials, such as penicillins and cephalosporins. Spread of ESBL/pAmpC resistance occurs via clonal and plasmid spread (Nikaido, 2009). ESBL/pAmpC producing bacteria are widely distributed in animals and humans, as reviewed by Ewers et al. (2012); Karanika et al. (2016), as well as in food (Leverstein-van Hall et al., 2011; Cohen Stuart et al., 2012; Kluytmans et al., 2013; Rasmussen et al., 2015; Randall et al., 2017) and in the environment, as reviewed by Huijbers et al. (2015b). In animals, a high prevalence of ESBL/pAmpC producing bacteria is found in broilers and broiler parents (Mesa et al., 2006; Smet et al., 2008; Dierikx et al., 2013a, b; Blaak et al., 2015; Huijbers et al., 2016; Dame-Korevaar et al., 2017), and a high level of heterogeneity in ESBL-genes and plasmids has been reported in the poultry production pyramid, as reviewed by Saliu et al. (2017).

Carriage of ESBL/pAmpC producing bacteria by humans is associated with living or working on broiler farms in several Dutch studies (Dierikx et al., 2013b; Huijbers et al., 2014, 2015a; van Hoek et al.,

2016; Dorado-Garcia et al., 2018). Transfer via the consumption of meat is indicated in some studies (Hijazi et al., 2016; Leverstein-van Hall et al., 2011; Kluytmans et al., 2013; Dorado-Garcia et al., 2018). However, in other studies this association was not observed (Leistner et al., 2013; Carmo et al., 2014; de Been et al., 2014).

The decrease in ESBL/pAmpC-*E. coli* prevalence in broilers reported in the Netherlands and in Denmark is most likely related to a reduction of antimicrobial usage (DANMAP, 2015; MARAN, 2018). The use of antimicrobials and the presence of ESBL/pAmpC producing bacteria, and more specific resistance against Extended Spectrum Cephalosporins (ESC), is associated with the use of third generation cephalosporins for example in hatcheries (Dutil et al., 2010; Bron et al., 2014; Baron et al., 2016; MARAN, 2018). However, even in the absence of antimicrobials ESBL/pAmpC producing bacteria are able to colonise chickens and the plasmids encoding for ESBL/pAmpC production are able to spread within a bacterial and animal population (Le Devendec et al., 2011; Fischer et al., 2014; Huijbers et al., 2016; Ceccarelli et al., 2017; Dame-Korevaar et al., 2017). Next to the use of antimicrobials, other drivers related to the structure of the poultry production pyramid and management on farms might contribute to the occurrence of resistance (Dorado-Garcia et al., 2016).

To control ESBL/pAmpC prevalence in broilers, the pyramidal structure of broiler production is of importance (Fig. 1). At the top of the production

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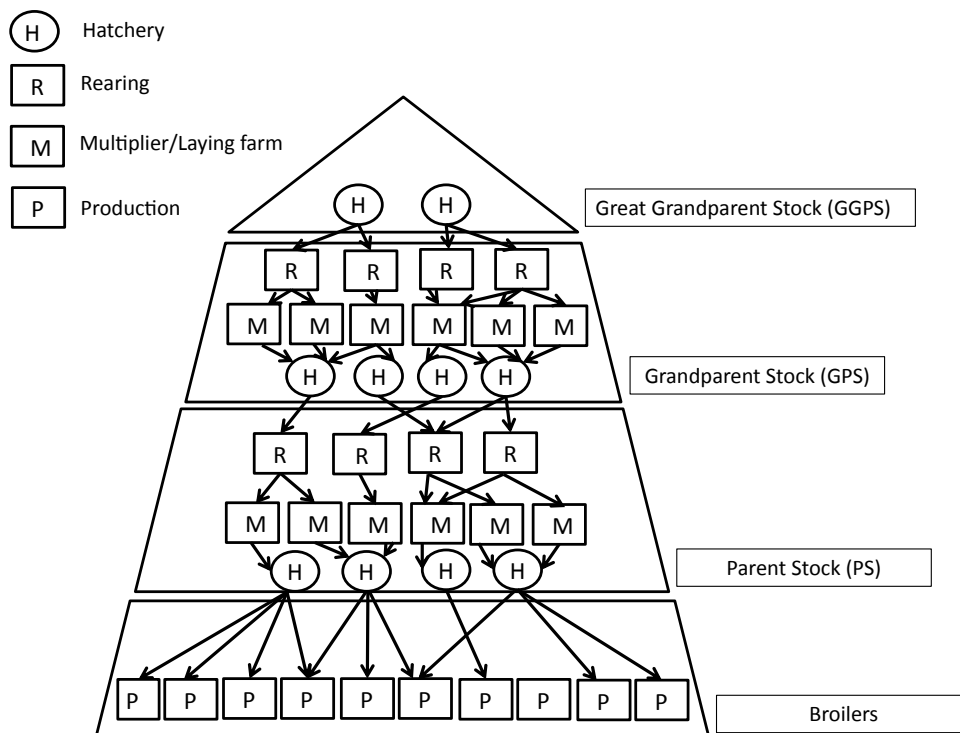


Fig. 1. Schematic view of the broiler production pyramid. The broiler production pyramid includes different levels; Great Grandparent Stock (GGPS) birds at the top of the pyramid, Grandparent Stock (GPS), Parent Stock (PS), and broilers at the bottom of the pyramid, with increasing numbers of farms from top to bottom. Levels in the pyramid are linked through hatcheries (H).

pyramid Great Grandparent Stock (GGPS) birds are produced by a few breeder companies at pedigree farms. The offspring of these GGPS are hatched at hatcheries and transported to Grandparent Stock (GPS) rearing farms. Around the age of 18 weeks these GPS are moved to GPS multiplier farms. These birds produce offspring which are the Parent Stock (PS) of the birds raised for meat production at broiler farms. Therefore, controlling ESBL/pAmpC prevalence in broilers requires taking into account possible transmission of ESBL/pAmpC producing bacteria throughout the entire pyramid, as has been described for *Salmonella* (Van Immerseel et al., 2009) and *Campylobacter* (Idris et al., 2006; Katsma et al., 2007) and was suggested for ESBL-*E. coli* (Borjesson et al., 2013b; Dierikx et al., 2013a).

The presence of ESBL/pAmpC producing bacteria in the different levels of the broiler production chain has been described in the past decennia. However, an overview of possible transmission routes of ESBL/pAmpC producing bacteria in the broiler production chain is lacking. This review aims to describe possible routes of transmission of ESBL/pAmpC producing bacteria described in the literature, because understanding these routes is a prerequisite for control. It includes four different types of transmission, which correspond to the structure of the poultry production pyramid: 1) transmission from generation to generation (e.g. parent to offspring), 2) transmission at hatcheries, 3) horizontal on farm transmission and 4) horizontal between farm and environmental transmission.

2. Methods

2.1. Search strategy

A systematic search in PubMed and CAB Abstracts was done, including articles until 26 April 2018. Three search terms were used: [poultry] AND [ESBL/AmpC] AND [spread]. Complete search terms, including synonyms, are given in Appendix 1. No limits were set on time.

2.2. Data selection

Duplicates were removed from the dataset before selection of useful articles. Selection was done in three steps. First and second selections were done using an online program (www.covidence.org), on the basis of title and abstract. The first selection was done using the following inclusion criteria: a)

the study concerns broilers or layers, turkeys or ducks, including results on chain, farm and animal level, b) the study concerns plasmid mediated resistance. The second selection was done using the following inclusion criteria: the study concerns ESBL/pAmpC producing bacteria in the broiler production pyramid. Relevant studies concerning layers, turkeys or ducks, were included when transmission routes described in these animals were also relevant in the broiler production chain. Studies were selected if isolates were typed as ESBL/pAmpC producing bacteria or if resistance against beta-lactam antimicrobials was reported. Beta-lactam antimicrobials were restricted to Extended Spectrum Cephalosporins (ESC), although a few articles reporting resistance against first or second generation cephalosporins were included as they contained additional information regarding possible transmission routes.

Third selection was based on full articles, available in pdf or hard copy, in Dutch, English or German language. In this selection a study was included if it suggested or described a certain route or mechanism of spread of ESBL/pAmpC producing bacteria in poultry, or if it mentioned risk factors or interventions on the occurrence of ESBL/pAmpC producing bacteria. Studies containing no primary data were excluded from further analysis, with the exception of some reviews containing information in addition to the selected articles. After the third selection duplicates missed in the first elimination were removed manually. The articles were then studied, the data was extracted from the full articles and included in the dataset. Data was categorised based on: 1) route: vertical transmission from generation to generation, transmission at hatcheries, horizontal on farm transmission or horizontal between farm and environmental transmission, 2) type of the study: observational or experimental, 3) type of results: quantitative or qualitative, 4) typing of the isolates: phenotypic or genotypic and 5) region of origin of the data. In addition, any mentioned risk factors and interventions were recorded.

2.3. Definition of transmission routes

2.3.1. Vertical transmission from generation to generation

Two types of vertical transmission from generation to generation are distinguished: true vertical transmission and apparent vertical transmission. True vertical transmission is transmission via ovarian or uterine infection, as is known for *Salmonella* Enteritidis (Guard-Petter, 2001; Buck et al., 2004). Apparent vertical transmission is transfer from the parent stock to the next

generation via the environment, for example via faecal contamination of the egg shell at the parent farm (Wilkinson, 1999). It is often impossible to distinguish apparent and true vertical transmission. Furthermore, the role of the hatchery between parents and offspring is difficult to untangle. In Section 4.1 all studies mentioning the role of the parents are discussed, studies describing the potential role of the hatcheries, as a link between generations, are discussed separately in Section 4.2.

2.3.2. Transmission at hatcheries

Transmission at the hatchery can originate from ESBL/pAmpC producing bacteria present in the environment of the hatchery or can originate from eggs of the supplying parent flocks carrying ESBL/pAmpC producing bacteria, leading to contamination of other eggs or newly hatched birds in the hatching units. In Section 4.2 all studies mentioning the role of the hatchery in transmission of ESBL/pAmpC producing bacteria are discussed.

2.3.3. Horizontal on farm transmission

Horizontal transmission on a farm occurs within and between flocks. Transmission can occur via direct physical or faecal contact between birds and via indirect contact, for example via humans, shared equipment, a contaminated poultry house, or other animals or vectors, such as flies. Here we exclude vertical transmission between parents and offspring, or contamination in a hatchery. Horizontal transmission between flocks at a farm can occur between both parallel and serially housed flocks. In Section 4.3 articles mentioning horizontal transmission on a farm are discussed.

2.3.4. Horizontal between farm and environmental transmission

Horizontal transmission between farms can occur via indirect contact, for example via humans, other animals, trucks or shared equipment or via the environment, at different levels of the poultry production chain. In Section 4.4 articles mentioning horizontal transmission between farms are discussed.

3. Results

In total 9212 articles were retrieved from PubMed and CAB Abstracts. During the first and second selection rounds 8576 articles were excluded, because they did not concern poultry, plasmid mediated resistance, or both. After the third selection round 103 articles, containing information on possible transmission routes, were included in the database for this review (Fig. 2, Table 1). Most articles report results from Europe (56/103), followed by Asia (25/103), North-America (6/103), Latin-America (6/103), Africa (5/103), and Oceania (1/103). The remaining 4 articles report results from more than one continent. Of the 103 articles, 98 articles report primary data. The other 5 articles are reviews (Hille et al., 2014; Olsen et al., 2014; Zurek and Ghosh, 2014; Ljubojevic et al., 2016; Wang et al., 2017) containing valuable additional information regarding possible transmission routes.

Transmission routes included in this review are categorised based on the observations and suggestions described by the authors. Some articles describe more than one possible transmission route or a single route in different types of poultry, resulting in a total of 133 descriptions of possible routes and 19 descriptions of risk factors. Of these 133 descriptions, 27 include vertical transmission from generation to generation, 19 transmission at hatcheries, 42 horizontal on farm transmission, and 45 horizontal between farm and environmental transmission. The vast majority of descriptions (122/133) originate from observational studies, 6 from experimental studies, and the remaining 5 from reviews. Most described or suggested routes are based on qualitative interpretation of data (106/133), whereas only 27/133 of the described routes are based on quantitative data. Studies from different regions suggest different transmission routes. The vertical transmission route and transmission at hatcheries is mostly suggested by descriptions including data from Europe (35/46), whereas only half (23/45) of the descriptions suggesting between farm and environmental transmission include data from Europe. In this review the region of data collection is reported. The routes are discussed in Section 4 and summarised in Table 1 and Fig. 3.

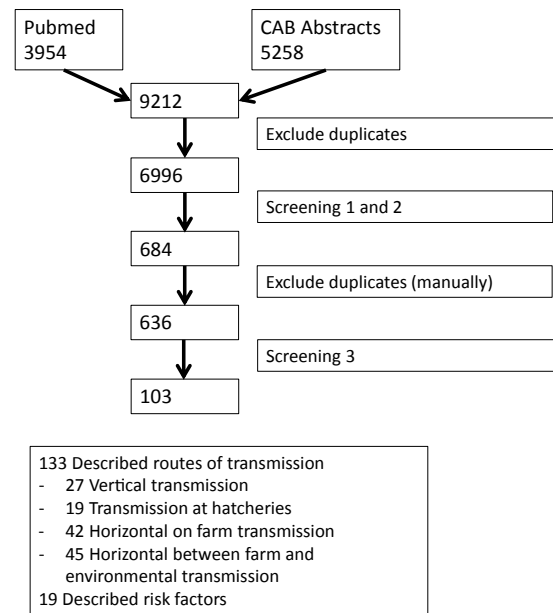


Fig. 2. Schematic view of included articles (n) per selection step, and the described routes of transmission ($n=133$) and risk factors ($n=19$) in the final included articles.

4. Routes of transmission

4.1. Vertical transmission from generation to generation

In a longitudinal study in Norway the odds for ESC-resistance in broilers increased 6-fold (OR 6.3; 95%CI 1.6–25.0) when more than two parent flocks were supplying the broiler flock. This could be explained by the increased probability of at least one of the parent flocks being positive. However, no direct association between the status of the supplying parent flock and the broiler flock was found (Mo et al., 2016). The probability of detecting ESBL-*Enterobacteriaceae* was decreased when chicks were produced at the farm (OR 0; 95%CI 0.00-0.91), suggesting reduced risk of vertical transmission without introduction of new chicks in the farm (Gay et al., 2018).

ESBL/pAmpC-*E. coli* isolates have been observed in different levels of the broiler production pyramid (Dierix et al., 2013a; Agerso et al., 2014; Nilsson et al., 2014; Zurfluh et al., 2014a, b; Projahn et al., 2018). The finding of genetically similar IncI1 plasmids associated with ESBL-*E. coli* (Zurfluh et al., 2014a, b), or highly related *E. coli* isolates carrying pAmpC gene *bla*_{CMY-2} (Nilsson et al., 2014) in different levels of the broiler production chain indicates vertical transmission and suggests a common source. Genetically similar or closely related resistant *E. coli* found in broilers and their broiler parents support the likelihood of vertical transmission (Bortolaia et al., 2010; Olsen et al., 2014; Projahn et al., 2018). However, introduction via an earlier event could also have occurred (Projahn et al., 2018), and many other factors, such as the hatchery, might be of influence (Hille et al., 2014).

The possibility of vertical transmission via eggs is shown by the detection of ESC-resistant *Enterobacteriaceae* on crushed decontaminated eggshells and eggshell surface of 7/186 broiler hatching eggs (Mezhoud et al., 2016). Moreover, genetically highly related *E. coli* isolates with ESBL gene *bla*_{CTX-M-1} were found in a parent flock and on their outer egg shells before decontamination of the eggs (Projahn et al., 2017). Furthermore, in a study on chicken table eggs, multiresistant *E. coli* was found on eggshells from conventional barns as well as from organic and domestic flocks (Alvarez-Fernandez et al., 2012).

Several observational studies suggest vertical transmission as explanation of the finding of ESC-resistance in birds not treated with antibiotics. The presence of ESBL/pAmpC producing bacteria in organic

Table 1
Included articles in the database, describing vertical transmission ($n = 27$), transmission at hatcheries ($n = 19$), horizontal on farm transmission ($n = 42$), horizontal between farm and environmental transmission ($n = 45$), or risk factors ($n = 19$) categorised per route on region of origin of data, type of study, type of data, type of study, type of results, typing of isolates.

Route	Region of data collection	n	Type study*	n	Type data	n	Typing isolates*	n	Articles**	n	Quantitative Results***
Vertical transmission from generation to generation	EU	21	O	23	qual	20	G	20	Agersø et al., 2014		
	Asia	1						0	Borjesson et al., 2013a,b		
	Africa	1							Bortolaia et al., 2010		
	Oceania	2							Carmo et al., 2014		
	> 1 continent	2							Cohen Stuart et al., 2012		
									Dierikx et al., 2013a		
									Dolejska et al., 2011		
									Mezhoud et al., 2016		
									Mo et al., 2014		
									Myrenas et al., 2018		
Transmission at hatcheries	EU	14	O	19	quant	3	G	2	Alvarez Fernandez et al., 2012		Higher frequencies of multiresistant <i>E. coli</i> on eggshells from conventional barns (95%) than from organic (30%) or domestic (20%) farms ($p < 0.05$)
	N-America	1						1	Gay et al., 2018		OR 0 (0.00-0.91) ESBL- <i>Enterobacteriaceae</i> occurrence if chicks are produced at the farm
	L-America	1							Mo et al., 2016		OR 6.3 (1.6-25) ESC-resistance if > 2 supplying parent flocks
	Asia	2	E	2	qual	2	P	2	Jimenez-Belenguier et al., 2016		
	Africa	1							Roth et al., 2017		
									Hille et al., 2014		
									Olsen et al., 2014		
									Bortolaia et al., 2010		
									Baron et al., 2018		
									Dierikx et al., 2013a		
								Osman et al., 2018			
								Ozaki et al., 2017			
								Projahn et al., 2017			
								Projahn et al., 2018			
								Schwaiger et al., 2013			
								Shahada et al., 2013			
								Weill et al., 2004			
								Baron et al., 2014 (4)			
											Layers and broilers: presence of <i>bla</i> _{CMX-2} differs between hatchery of origin ($p < 0.05$); Layers and broilers: <i>in ovo</i> treatment with ceftiofur higher prevalence of ESC-resistance (35.1 vs 11.2 for broilers, 46.4 vs 21.9 for layers)
											Higher prevalence ESC- resistance in broiler flocks if treatment with ceftiofur in hatchery (35%) vs no ceftiofur treatment (25%) ($p = 0.05$)
											Decreasing prevalence of ESC-resistant <i>E. coli</i> with age ($p < 0.05$)
											OR 0.94 (0.91-0.97) non-susceptible isolates with increasing age (weekly)
											Similar proportions of ESC-resistant isolates in pullet and layer flocks originating from the same hatcheries ($p = 0.002$)
											Occurrence of ESC-resistance differs between hatchery of origin ($p < 0.01$)

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Table 1 (continued)

Route	Region of data collection	n	Type study*	n	Type data	n	Typing isolates*	n	Articles**	n	Quantitative Results***
Horizontal on farm transmission	EU	32	O	38	qual	28	G	20	Agersø et al., 2014, Blaak et al., 2014 (2)	8	
	N-America	1					P		Borjesson et al., 2013a		
	L-America	1							Daehre et al., 2017		
	Asia	5							Dierikx et al., 2013a		
	Africa	2							Hering et al., 2016		
	> 1 continent	1							Ho et al., 2015		
									Huijbers et al., 2016		
									Laube et al., 2013 (3)		
									Lu et al., 2010		
									Mattello et al., 2015		
									Mezhoud et al., 2015		
									Nguyen et al., 2016		
								Oguttu et al., 2008			
								Persoons et al., 2010 (3)			
								Projahn et al., 2018			
								Reich et al., 2013			
								Schwaiger et al., 2013			
								Smith et al., 2017			
								Sola-Gines et al., 2015			
								Stokes et al., 2012			
								Zurfluh et al., 2014a,b			
					quant	10	G	8	Boulianne et al., 2016		Higher prevalence of ESC-resistance if growing turkey on previous used chicken litter (p = 0.02) (7 vs 0% resistant isolates per flock)
							P	2	Huijbers et al., 2016		RO of ESBL/pAmpC in organic broilers 1.70 (0.55-5.25)
									Jones et al., 2013 (5)		OR 0.44 (0.17-1.14) ESC-resistant <i>E. coli</i> in fattening turkeys if flocks are compartmentalised
											OR 73.05 (5.93 – 900.12) ESC-resistant <i>E. coli</i> in breeding turkeys if keeping birds in one house
											OR 0.15 (0.03-0.78) ESC-resistant <i>E. coli</i> in breeding turkeys if other domestic animals are absent on farm
											OR 2.8 (1.36-5.76) ESC-resistant <i>E. coli</i> in fattening turkey if staff working with other livestock
											OR 0.47 (0.22 – 1.02) ESC-resistant <i>E. coli</i> in fattening turkey if staff wear gloves
											OR 12.7 (4.8-33.5) ESC-resistant <i>E. coli</i> in broiler flock if in previous flock ESC-resistance was present
											OR 0.1 (0.03-0.6) ESC-resistant <i>E. coli</i> in broiler flock if disinfecting floor in between production rounds
											OR 4.82 (1.27-18.27) presence ESBL- <i>E. coli</i> on chicken farm if fish ponds are present
			E	3	qual	2	G	2	Nguyen et al., 2015		
									Hiroi et al., 2012		
									Mo et al., 2017		
					quant	1	G	1	Ceccarelli et al., 2017		Transmission rate (β) of ESBL- <i>E. coli</i> in SPF broilers 1.33 (0.600-2.51) per day
			R	1	qual	1		1	Zurek and Ghosh, 2014		

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Table 1 (continued)

Route	Region of data collection		Type study*		Type data		Typing isolates*		Articles**		Quantitative Results***
	n	n	n	n	n	n	n	n	n	n	
Horizontal between farm and environmental transmission	EU	23	O	42	qual	38	G	30	Amadi et al., 2015 (2)		
	N-America	4					P	8	Antilles et al., 2015 Aw et al., 2015		
	L-America	4							Blaak et al., 2014 (2)		
	Asia	10							Blaak et al., 2015 (4)		
	Africa	1							Bonnedahl et al., 2015		
	> 1 continent	3							Borges et al., 2017 Cohen Stuart et al., 2012 Colomer-Lluch et al., 2011		
									Daehre et al., 2017 Friese et al., 2013 Gao et al., 2014 Hasan et al., 2012 Hassan et al., 2016 Hassan, 2015		
									Horton et al., 2011 Jiang et al., 2011 Kim et al., 2005 Laube et al., 2014 (2)		
									Ma et al., 2012 Mathys et al., 2017 Nhung et al., 2015 Oh et al., 2015 Oluduro, 2012		
									Pohjola et al., 2016 Projahn et al., 2018 Schaufler et al., 2016 Shahbaz Raza et al., 2017		
									Siemon et al., 2007 Stedt et al., 2015 Vergara et al., 2017 Zurfluh et al., 2014a Chen et al., 2016		
					quant	4	G	4	Jones et al., 2013 Mo et al., 2016		Higher proportion of ESBL-E. coli in rivers in regions where more chickens are raised (33.8 vs 21.1 %) (p = 0.013) OR 2.6 (1.16-5.83) ESC-resistant E. coli on fattening turkey farms if neighbour farms with pigs OR 9.3 (1.6-55.1) ESC-resistant E. coli if transport personnel enter the room where broilers are raised Wild birds form urban origin associated with the presence of resistant E. coli (p < 0.01)
									Parker et al., 2016 Duijkeren et al., 2015 Ljubojevic et al., 2016 Wang et al., 2017		
	E	1			qual	1	G	1			
	R	2			qual	2					

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Table 1 (continued)

Route	Region of data collection		Type study*		Type data		Typing isolates*		Articles**	Quantitative Results***	
	n		n		n		n				
Risk factors	EU	5	O	17	qual	4	G	4	Fitch et al., 2016 Li et al., 2014 Samanta et al., 2015 Xu et al., 2014	Higher percentage of antimicrobial resistant bacteria in production versus household birds (p < 0.01) OR 9.55 (6.14 – 14.85) ESBL-Enterobacteriaceae presence in broiler versus layer farms. Prevalence higher in broiler (87%) versus layer farms (42%) Prevalence of CTX-M-E. coli lower in backyard chickens (13.9%) compared to chickens on large-scale farms (71.1%) (p < 0.05) OR 12.72 (1.25–671.77) ESBL-Enterobacteriaceae occurrence in broilers in recently built premises (> 1999) Rates multi-resistant Enterobacteriaceae lower in organic chicken meat (41.7%) compared to conventional chicken meat (63.3%) (p = 0.0197) OR 13.02 (1.89–89.61) presence of ESBL-E. coli if purchase of day old chicks from other sources than industrial hatchery Risk of presence of ceftiofur resistant E. coli: OR 3.47 (1.05–11.50) if no acidification of the drinking water OR 8.25 (1.39–48.80) if > 3 feed changes per cycle OR between 1.02 and 655.89 for different hatcheries of origin OR 9.14 (2.30–36.41) if breed is Ross OR between 5.08–8.04 if litter material other than wood curls OR 5.18 (1.55–17.29) if clean hygienic condition of medicinal treatment reservoir Prevalence of ESBL-Salmonella in retail chicken varies between Chinese provinces (1.6 – 50%) (p < 0.05) and higher percentage of ESBL-Salmonella isolates found in autumn (20%) compared to spring (7.9%) (p < 0.05) Prevalence of ESBL-E. coli in retail chicken meat varies between UK regions (40.6–53.1 vs 75.0–80.6%) (p = 0.001) Lower percentage of ESC-resistant Salmonella in farms that changed from conventional to organic practice compared to conventional poultry houses (p = 0.043) Prevalence of ESBL-Salmonella in retail chicken varies between Chinese regions (0–24.64%) (p < 0.05) and higher percentage of ESBL-Salmonella isolates found in autumn (24.64%) compared to spring (7.44%) and winter (6.12%) (p < 0.05) Lower median ESBL-E. coli excretion (CFU/g faeces) (1.17–2.22 vs 5.68 CFU) (p < 0.001) and lower transmission rate (β) (0.669–0.331 vs ∞) (p < 0.001) if animals treated with competitive exclusion product prior to ESBL challenge Lower caecal ESBL-E. coli colonisation (cfu/g caecal content) if broilers are treated with competitive exclusion product (p < 0.001)	
	N-America	1									
	L-America	2									
	Asia	10									
	Africa	1									
						quant	13	G	7		Braykov et al., 2016
								P	6		Brower et al., 2017
											Bui et al., 2018
											Gay et al., 2018
											Miranda et al., 2008
									Nguyen et al., 2015		
									Persoons et al., 2011		
									Qiao et al., 2017 (2)		
									Randall et al., 2017		
									Sapkota et al., 2014		
									Wu et al., 2013 (2)		
					quant	2	G	2	Ceccarelli et al., 2017		
			E	2					Ntutio et al., 2013		

* O = observational, E = experimental, R = review.

** G = genotypic, P = phenotypic. For reviews (R) typing of isolates is not included.

*** n, if > 1 transmission route reported.

**** OR = Odds Ratio (95% CI).

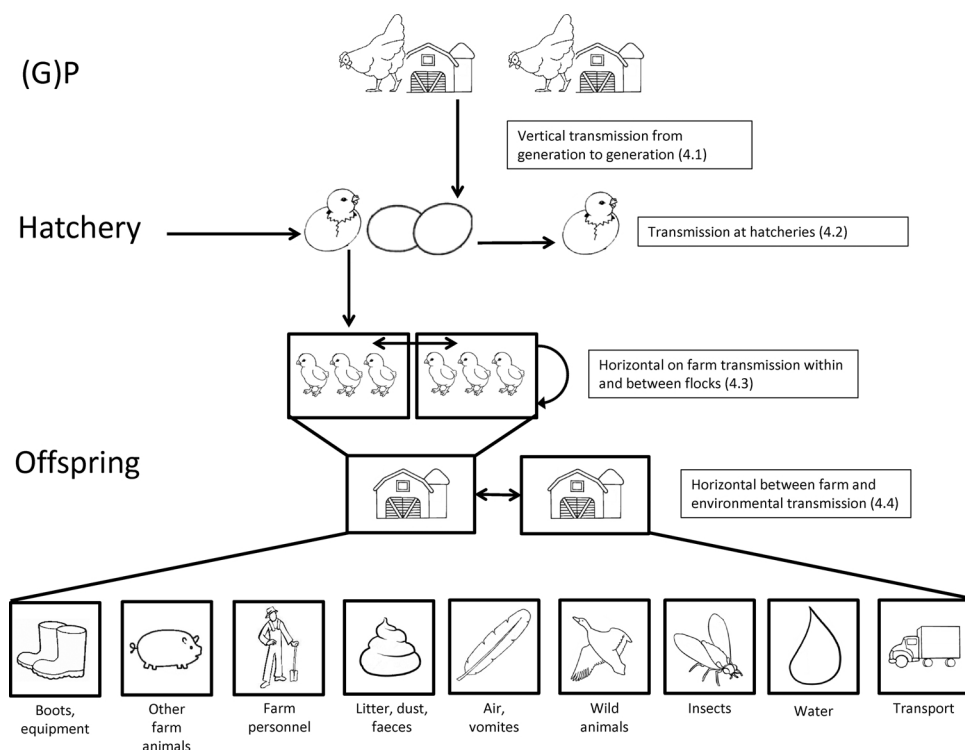


Fig. 3. Schematic view of possible transmission routes of ESBL/pAmpC producing bacteria in the broiler production pyramid, as described in Section 4.1 – 4.4, including Great Grandparent, Grandparent and Parent Stock ((G)P), hatcheries and their offspring. At each level farms, flocks or individual birds can be part of the transmission route, as well as the environment.

broiler meat originating from farms without antibiotic usage was explained by the possibility of vertical transmission resulting in introduction of ESBL carrying one-day old broilers into the organic farms (Cohen Stuart et al., 2012). Moreover, in countries like Denmark, Norway, Sweden and Finland, where cephalosporins have never been used in poultry, ESC-resistant *E. coli* were found in different levels of the production pyramid. Use of cephalosporins at hatcheries in the supplying countries was suggested to be the cause of the presence of ESC-resistant *E. coli* in (grand)parent stock, which spread vertically to their offspring via the import of breeding animals and hatching eggs (Borjesson et al., 2013a, b; Carmo et al., 2014; Mo et al., 2014; Paivarinta et al., 2016; Myrenas et al., 2018). The finding of *E. coli*, resistant to several antimicrobials, in one-day old broiler chicks (Jimenez-Belenguer et al., 2016; Roth et al., 2017; Yossapol et al., 2017) and ampicillin resistant *E. coli* in young broilers (Obeng et al., 2014) suggest vertical transmission from breeder birds to offspring. Moreover, ampicillin resistant *E. coli* found in young pullets (Obeng et al., 2014) and clonally related ESBL-*E. coli* isolates in different turkey farms supplied by the same producer, support that vertical transmission between generations can occur in poultry (Dolejska et al., 2011).

4.2. Transmission at hatcheries

The occurrence of ESC-resistant *E. coli* in broilers and layers is associated with the supplying hatchery (Persoons et al., 2011; Baron et al., 2014). Moreover, similar proportions of ESC-resistant isolates in pullet and layer flocks originating from the same hatcheries ($p = 0.002$) indicate a relationship between ESC-resistance and the supplying hatchery (Chauvin et al., 2013). The prevalence of ESC-resistant *E. coli* is higher at young ages in broilers and layer hens ($p < 0.05$) (Braykov et al., 2016) and in pullets (OR 0.94; 95%CI 0.91-0.97) (Chauvin et al., 2013), which indicates that colonisation occurs mainly at a young age and suggests that the hatchery has a role in the spread of ESC-resistant *E. coli*.

The relationship between hatchery and ESC resistance could be the result of a selection due to antimicrobial treatment at the hatchery.

Treatment in the hatchery with ceftiofur *in ovo* resulted in a higher prevalence of ESC-resistant isolates in broiler and layer flocks compared to non-treated flocks at the age of 0–7 days (35.1% versus 11.2% for broilers and 46.4% versus 21.9% for layers) (Baron et al., 2014). Treatment with ceftiofur in the hatchery led to a higher prevalence of ESC-resistance in Canadian broiler chicken flocks ($p = 0.05$) (Boulianne et al., 2016). However, antimicrobial treatment in the hatchery is not common practice in all countries.

The presence of *E. coli* with AmpC gene *bla_{CMY-2}* in the hatchery units and in one-day old birds (Dierikx et al., 2013a) and genetically related isolates in the hatchery environment and the fattening flock (Projahn et al., 2018) suggests that colonisation of young broilers can occur at the hatchery. Investigation of ESBL/pAmpC bacteria in a German hatchery showed presence of ESBL/pAmpC-*Enterobacteriaceae* on the surface of eggs from ESBL/pAmpC positive broiler parent flocks before disinfection (5/280) and even after disinfection (1/280). At hatch ESBL/pAmpC-*Enterobacteriaceae* were found in dust, crushed egg shell and environmental samples. Although the proportion of positive samples was low and all hatchlings were negative for ESBL/pAmpC producing bacteria, the existence of resistant *Enterobacteriaceae* in the hatching environment being phylogenetically related with the ESBL/pAmpC-*Enterobacteriaceae* present in the parent flock indicates transmission via the hatchery (Projahn et al., 2017). Broiler flocks from different rounds and different farms but from the same hatchery showed genetically similar ampicillin- or ESC-resistant *E. coli* types, indicating the hatchery as common source (Bortolaia et al., 2010; Shahada et al., 2013; Schwaiger et al., 2013; Ozaki et al., 2017; Baron et al., 2018). Possible transmission from hatchery to farm was also found in a French study, where one single *Salmonella* was identified as the supplier for six chicken farms on which *Salmonella enterica* with ESBL gene *bla_{CTX-M-9}* was found (Weill et al., 2004).

In another study different resistance genes were detected in hatchlings versus their hatchery environment, indicating another source (Osman et al., 2018). Moreover, the high similarity of plasmids in broiler flocks and in the supplying hatchery, but also to plasmids earlier reported in other regions and animal species makes it difficult to determine the origin of the contamination (Baron et al., 2018).

4.3. Horizontal on farm transmission

4.3.1. Transmission within flocks

The basic reproduction ratio (R_0) of ESBL/pAmpC-*E. coli* in an organic broiler flock, thus without the use of antibiotics, was 1.70 (95%CI 0.55–5.25) (Huijbers et al., 2016), indicating that ESBL/pAmpC-*E. coli* are able to persist in the broiler flock without a selective advantage. The probability of being ESBL/pAmpC-*E. coli* positive depends on both the presence of ESBL/pAmpC-*E. coli* positive birds and ESBL/pAmpC-*E. coli* present in the environment of the broiler flock (Huijbers et al., 2016). Also, experimental transmission studies show that ESBL/pAmpC-*E. coli* are able to spread between young specific pathogen free (SPF) birds without selective advantage (β of 1.33 per day (95%CI 0.600–2.51) (Ceccarelli et al., 2017). Housing management may influence the presence of resistant bacteria in a flock: a study on fattening turkeys showed that compartmentalisation of flocks decreased the presence of ESC-resistant *E. coli* in fattening turkeys, whereas keeping breeding turkeys in one house, from day-old to depopulation, increased the probability that ESC-resistant *E. coli* was present (OR 73.05; 95%CI 5.93–900.12), although only a few turkey flocks were included in the analysis (Jones et al., 2013).

The finding of similar plasmid-gene combinations within broiler and broiler breeder flocks, although in different *E. coli* types, suggests that within a flock horizontal spread of plasmids encoding ESBL/pAmpC-genes occurs (Zurfluh et al., 2014b). Also reproduction could play a role in spread of ESBL/pAmpC producing bacteria, since ESBL-*E. coli* were found in the reproduction tract of broiler breeder roosters, possibly as a result of faecal contamination (Mezhoud et al., 2015). Genetically related isolates found in chicken samples from the same farm, pen or market can be the result of horizontal transmission of ESC-resistant bacteria between animals (Lu et al., 2010; Ho et al., 2015).

4.3.2. Transmission between subsequent flocks in the same house

In a Norwegian study the presence of ESC-resistant *E. coli* in broiler flocks without antimicrobial usage was associated with the presence of ESC-resistance in the previous flock in the same house (OR 12.7; 95%CI 4.8–33.5) and disinfecting the floor between two production rounds was associated with a decreased presence of ESC-resistant *E. coli* in the subsequent flock (OR 0.1; 95%CI 0.03–0.6) (Mo et al., 2016). Transmission between flocks might occur via litter, dust, or faeces (Laube et al., 2013). In turkeys, prevalence of ESC-resistant *E. coli* isolates was higher when turkeys were transferred to litter previously used by chickens ($p = 0.02$) (Boulianne et al., 2016). A lab study showed that transfer of plasmids carrying *bla*_{CMY-2} occurs between bacteria, at temperatures down to 25 °C, which might enable the plasmids to spread in the broiler production environment (Mo et al., 2017).

The presence of phylogenetically similar ESBL/pAmpC-*E. coli* in broilers at the end of the previous round, in the broiler house at day 1 before arrival and in the broilers and their environment during the subsequent round (Huijbers et al., 2016; Daehre et al., 2017) and the persistence of resistant bacteria in consecutive rounds (Persoons et al., 2010; Reich et al., 2013) indicate that these bacteria can transmit between subsequent flocks.

Insufficient cleaning might lead to persistence of ESBL/pAmpC producing bacteria in the poultry house environment and play a role in the persistence of ESBL/pAmpC-genes on a farm (Laube et al., 2013; Mattiello et al., 2015). In an experimental study antibiotic treatment of flocks raised in broiler houses that tested ESBL positive in previous rounds did result in ESBL-*E. coli* colonisation, whereas no ESBL-*E. coli* was found in a flock treated with antibiotics and raised in a clean laboratory animal room (Hiroi et al., 2012), indicating that raising ESBL-*E. coli* free broilers in hygienic circumstances can prevent their colonisation with ESBL/pAmpC producing bacteria. However, even after cleaning and disinfection, carry-over at farm level from flock to flock can occur and might result in recirculation at farm level (Oguttu et al., 2008; Schwaiger et al., 2013; Daehre et al., 2017), also depending on

the fitness of the strain (Agersø et al., 2014; Huijbers et al., 2016). Colonisation of young birds might be followed by a rapid increase of ESBL/pAmpC prevalence in a broiler flock (Dierikx et al., 2013a). Horizontal transmission between subsequent flocks might contribute, next to vertical transmission, to the high prevalence of ESBL/pAmpC producing bacteria in countries, where no antibiotics have been used (Borjesson et al., 2013a).

4.3.3. Transmission between houses or parallel flocks on the same farm

Transmission between flocks kept in parallel might occur via dust and faeces on equipment, clothes or shoes (Laube et al., 2013) and presence of farm personnel and other farm animals was suggested as possible explanation for transmission (Persoons et al., 2010). Transmission via farm personnel can be reduced by hygiene measures; a study including turkeys showed that staff wearing gloves reduced the risk of occurrence of ESC-resistant *E. coli* in fattening turkeys (OR 0.47; 95%CI 0.22–1.02) (Jones et al., 2013). Farm personnel working with other livestock was positively associated with the presence of ESC-resistant *E. coli* at fattening turkey farms (OR 2.8; 95%CI 1.36–5.76) (Jones et al., 2013). The absence of other domestic farm animals on a turkey farm was associated with decreasing presence of ESC-resistant *E. coli* in breeding turkeys (OR 0.15; 95%CI 0.03–0.78) (Jones et al., 2013), whereas the presence of fish ponds was associated with increasing presence of ESBL-*E. coli* on a chicken farm (OR 4.82; 95%CI 1.27–18.27) (Nguyen et al., 2015). The finding of ESBL/AmpC-*Salmonella* in fish and poultry meat suggests that interaction between animal species for example via faecal contact may lead to spread of bacteria between different hosts (Nguyen et al., 2016).

Genetically related ESBL-*E. coli* strains from different barns at the same farm suggest transmission between flocks at the same farm (Projahn et al., 2018). Furthermore, investigation at German broiler farms showed that flocks kept in parallel are not independent, as the number of ESC-resistant samples was comparable between flocks on the same farm (Hering et al., 2016). However, these findings can also be explained by a similar source of the birds such as the hatchery or breeding flock.

Transmission via other animal species can occur via a shared environment. The finding of pCTX-like plasmids in *E. coli* with ESBL gene *bla*_{CTX-M-14} in cattle, turkeys and humans (Stokes et al., 2012) and *E. coli* with ESBL gene *bla*_{CTX-M-1} on ST3-Inc1 plasmids in chicken, cattle, pig and river water samples (Zurfluh et al., 2014a) suggests that plasmids can be transmitted between food producing animals and the environment.

Several studies have shown the presence of resistant bacteria in insects (Zurek and Ghosh, 2014). ESBL/AmpC-*E. coli* isolates were found in wild birds and flies (Smith et al., 2017). Similar ESBL-*E. coli* genotypes in flies and isolates selected from manure and rinse water at layer and broiler farms (Blaak et al., 2014), and flies captured at a broiler farm at different sampling times carrying the same type of ESBL-*E. coli* (Sola-Gines et al., 2015), show that it is likely that flies can act as a vector between animals facilitating the dissemination of ESBL/pAmpC-*E. coli*.

4.4. Horizontal between farm and environmental transmission

Several vehicles might facilitate between farm transmission. Transport personnel entering the farm was positively associated with the presence of ESC-resistant *E. coli* in broiler flocks (OR 9.3; 95%CI 1.6–55.1), suggesting their role in cross contamination between farms (Mo et al., 2016). Another source of between farm transmission might be environmental contamination through animals on neighbouring farms. On fattening turkey farms, the presence of ESC-resistant *E. coli* was positively associated with having neighbouring farms with pigs (OR 2.6; 95%CI 1.16–5.83) (Jones et al., 2013). Cattle grazing on a neighbouring pasture were suggested as possible source of ESC-resistant *Salmonella* found on a free-range poultry farm (Siemon et al., 2007).

Also backyard poultry with outdoor access were considered a potential reservoir of pAmpC-*E. coli* (Pohjola et al., 2016).

Farms positive for ESC-resistant bacteria can transmit these bacteria to their environment. Similar profiles of *E. coli* isolates found in samples from barn air and ambient air (50 m downwind), slurry and ground surfaces outside the barn were found (Laube et al., 2014). Moreover, closely related ESBL/AmpC-*E. coli* strains found in faeces and pasture and soil surrounding the ventilation exhausting air (Daehre et al., 2017), and identical ESBL-*E. coli* isolates found in poultry faeces and environmental samples from the same farm indicate potential transmission from broiler and layer farms to the environment outside the barn (Blaak et al., 2015).

Transmission between farms via transport crates and trucks is suggested by the finding of ESC-resistant *E. coli* on trays used for transport of both conventional and free-range eggs (Aw et al., 2015). ESBL-*E. coli* isolates found on a transportation truck and the litter and faeces of the connected fattening flock clustered together in MLST analysis, indicating that transmission can occur via the transportation system (Projahn et al., 2018).

Fomites, such as feathers, may spread resistant bacteria further from farms to their surroundings (Kim et al., 2005). Furthermore, poultry litter used as fertiliser, containing resistant *E. coli*, can contaminate soil, surface and ground water (Ljubojevic et al., 2016). The finding of ESBL/pAmpC-*E. coli* in broiler faeces, slurry and in the fields fertilised within 6 weeks before the sampling indicates that transmission through poultry litter is a potential route of spread and may contaminate animal farms in the neighbourhood (Friese et al., 2013). A wide variation in levels of ESBL-*E. coli* excretion is found between cattle, pigs and chickens. Therefore, depending on the housing management, for example if the animals have access to the outside, different animal species may vary in their contribution to environmental contamination (Horton et al., 2011).

The finding of similar ESBL-*E. coli* genotypes in rinse water, waste water, surface water and in the manure at layer and broiler farms indicates that transmission of ESBL-*E. coli* via contaminated water may occur (Blaak et al., 2014, 2015). Important vehicles for this spread include drinking water (Jiang et al., 2011), water troughs (Hassan, 2015) and duck swimming pools contaminated with faeces (Ma et al., 2012). A natural watercourse, such as a river, may also play a role in environmental transmission. Presence of ESBL-*E. coli* in river water was found to be higher in regions with large numbers of chickens being raised compared to regions with lower numbers of chickens being raised ($p = 0.013$) (Chen et al., 2016). Similar isolates from the river and faecal samples indicate that ESBL-*E. coli* can spread, probably via waste water, to the environment (Gao et al., 2014; Zurfluh et al., 2014a) and possibly to other farms.

Resistant bacteria can also be transmitted via wild birds that share the same environment (Hasan et al., 2012; Amadi et al., 2015; Hasan et al., 2016). ESBL-*E. coli* isolates from wild birds, humans, companion animals and the environment showed high similarity, suggesting an exchange of resistant genes between hosts sharing the same environment (Stedt et al., 2015; Schaufler et al., 2016). Although resistant *E. coli* were found in a higher number of wild birds from urban compared to rural origin ($p < 0.01$) (Parker et al., 2016), migration of wild birds utilising both urban and rural areas might result in spread of ESC-resistance. Moreover, wild birds can serve as a reservoir of ESC-resistant bacteria (Borges et al., 2017) and potentially transmit them over long distances via migration (Antilles et al., 2015; Oh, et al., 2015; Mathys et al., 2017; Shahbaz Raza et al., 2017; Vergara et al., 2017). However, others have concluded that local dissemination in a shared environment is more important for the presence of resistance genes in wild birds than migration of the birds (Bonnedahl et al., 2015). Besides transmission via wild birds, other wild animals might play a role (Wang et al., 2017), for example rats (Nhung et al., 2015) and bats (Oluduro, 2012) are indicated as sources of resistant *E. coli*. An experiment with 8-week old

SPF mice failed, however, to demonstrate persistence of avian ESBL-*E. coli* strains in mice (Duijkeren et al., 2015).

Bacteriophages present in the animal environment have been found to carry ESBL genes suggesting, that they may help maintenance and horizontal transfer of antimicrobial resistant genes in the animal environment (Colomer-Lluch et al., 2011).

Transmission of ESC-resistant bacteria from the environment to farms was also suggested as explanation for the presence of resistant bacteria in both free-range and organic chickens that had not received antibiotics (Cohen Stuart et al., 2012; Amadi et al., 2015).

4.5. Miscellaneous risk factors

This review focusses primarily on transmission routes in the broiler production pyramid. However, also risk factors and interventions for the presence of ESC-resistant bacteria are mentioned in the selected articles, and are reported in this section.

Organic and backyard farms tended to have a lower occurrence of resistant bacteria compared to conventional farms (Miranda et al., 2008; Samanta et al., 2015; Bui et al., 2017). Farms that changed from conventional to organic practice showed a decrease in ESC-resistant isolates (Sapkota et al., 2014). Commercially kept chickens showed higher percentages of resistance than non-commercially kept birds in Ecuador ($p < 0.01$) (Braykov et al., 2016), and in India the prevalence of ESBL-*Enterobacteriaceae* was higher in broiler farms compared to layer farms (OR 9.55; 95%CI 6.14–14.85) (Brower et al., 2017). These differences between production systems were most likely caused by both the level of antibiotic use and by bird density. At farm level in Vietnam, the purchase of one-day old chickens from sources other than industrial hatcheries was associated with the presence of ESBL-*E. coli* (OR 13.02; 95%CI 1.89–89.61) (Nguyen et al., 2015). Presence of ESBL-*Enterobacteriaceae* at broiler farms in Reunion was associated with recently built premises, possibly confounded by antibiotic use which might be higher in modern farms (Gay et al., 2018).

Prevalence of ESBL-*E. coli* and ESBL-*Salmonella* in retail chickens varied between regions (Wu et al., 2013; Qiao et al., 2017; Randall et al., 2017) possibly depending on different farm practices (Wu et al., 2013; Xu et al., 2014). Chicken carcasses from supermarkets from different regions in China showed the lowest prevalence in the region with a low human population density and mainly free ranging chickens. The highest prevalence was found in Beijing, where chickens were raised in high density and antimicrobials were used (Xu et al., 2014). Trade of poultry and poultry products might have contributed to the spread of resistant bacteria in Brazil, where genetically related ESBL producing *Salmonella*, carrying variants of *bla*_{CTX-M}, were found in different regions (Fitch et al., 2016).

Moreover, season might also influence prevalence, with higher percentages of ESBL producing bacteria in retail chicken found in autumn, compared to spring ($p < 0.05$) (Wu et al., 2013; Qiao et al., 2017) and winter ($p < 0.05$) (Wu et al., 2013). Possibly there was a relationship between frequently occurring epidemic poultry diseases in autumn and consequently more antibiotic usage (Wu et al., 2013).

A Belgian study showed that besides antimicrobial use, no acidification of the drinking water, more than three feed changes per cycle, hatchery of origin, breed and litter material are associated with the presence of ESC-resistant *E. coli*. Strikingly, a clean hygienic condition of the reservoir for medicinal treatment increased the risk of presence of ESC-resistant *E. coli* (Persoons et al., 2011). On the other hand, at a farm with no clearance of faeces higher numbers of ESBL-*E. coli* isolates were found compared to farms where faeces was cleared (Li et al., 2014), showing that poor farm hygiene may facilitate the occurrence and transfer of resistant bacteria. Possibly, risk factors as hygiene, drinking water and litter type might influence the microbiome and consequently the ability of ESC-resistant bacteria to colonise the gut (Persoons et al., 2011). Supplying a competitive exclusion product to broilers can

reduce colonisation of ESBL-*E. coli* ($p < 0.001$) (Nuotio et al., 2013), and decrease excretion ($p < 0.001$) and transmission ($p < 0.001$) of ESBL-*E. coli* during the first two weeks of life (Ceccarelli et al., 2017).

5. Discussion and conclusion

Four possible transmission routes of ESC-resistant bacteria in the broiler production pyramid are discussed in this review: 1) vertical transmission from generation to generation (e.g. parent to offspring), 2) transmission at hatcheries, 3) horizontal on farm transmission and 4) horizontal between farm and environmental transmission. Evidence of the existence and information on the magnitude of transmission along these transmission routes is, however, scarce and mainly based on observational studies. Only 27 of 133 described routes have quantified probabilities of transmission along one of the four routes identified. Due to a lack of quantitative data, a meta-analysis could not be performed, neither was it possible to quantify the level of evidence of the four transmission routes. Moreover, the general lack of quantitative results did not allow for a proper assessment of bias. Only a few experimental studies investigated the described routes, therefore hardly any causal evidence is found.

In order to find possible interventions to control ESBL/pAmpC prevalence and spread in the broiler production pyramid, it is important to determine the existence of transmission routes, and to quantify the magnitude of spread along the different transmission routes.

Although no direct relationship between the status of the parent flock and their offspring is reported, the presence of genetically related resistant isolates in different levels of the production chain (Bortolaia et al., 2010; Nilsson et al., 2014; Olsen et al., 2014; Zurfluh et al., 2014a, b; Projahn et al., 2018) and the presence of ESBL/pAmpC producing bacteria on farms and in countries, where no cephalosporins have been used (Cohen Stuart et al., 2012; Borjesson et al., 2013a, b; Carmo et al., 2014; Mo et al., 2014; Paivarinta et al., 2016; Myrenas et al., 2018), suggests that transmission between generations may occur. A possible route is via egg shells carrying ESBL/pAmpC producing bacteria (Mezhoud et al., 2016; Projahn et al., 2017) where the contaminated egg shells can result in colonisation of the offspring. It is, however, difficult to untangle transmission from parent to offspring from contamination in the hatcheries. Even low numbers of contaminated eggs might result in transmission from parent stock to the next generation, and therefore the magnitude of apparent vertical transmission might be overestimated, and contamination due to transmission at the hatchery underestimated. Therefore, we need both quantification of the probability of contamination from parent to offspring, as quantification of transmission among birds, as done in earlier studies (Ceccarelli et al., 2017). No transmission was observed in a field study where eggs from a contaminated parent flock were collected and broilers were hatched aiming to quantify vertical transmission. However, the number of eggs and the ESBL/pAmpC-*E. coli* prevalence in the parent flock were low (Dame-Korevaar et al., 2017). These kinds of studies with larger numbers of eggs are, however, feasible and can be performed to quantify transmission between generations. This can also be studied in experimental studies by hatching offspring of contaminated hens.

None of the included studies quantified the transmission occurring at the hatchery, but the available literature indicates the importance of spread via the hatchery. After introduction of resistant strains originating from parent stock they may spread to the hatchery inventory and further contaminate eggs or newly hatched birds from ESBL/pAmpC-free parent stock. Treatment at the hatchery leads to selection of resistant strains, resulting in an increased probability of colonisation (Baron et al., 2014; Boulianne et al., 2016). Quantification of the role of hatcheries is difficult but can be studied by zooming into specific parts of the route. For example, experimentally determining the transmission from contaminated eggs or the hatchery environment to hatchlings is possible in research facilities.

Strict hygiene measures might reduce the risk of recirculation at farm level, although in several studies even intensive cleaning and disinfection did not result in elimination of resistant strains (Oguttu et al., 2008; Schwaiger et al., 2013; Daehre et al., 2017). This might be caused by the presence of other, unknown sources of ESBL/pAmpC producing bacteria or indirect transmission at poultry farms, enabling transmission between flocks kept in parallel. Transmission between parallel and consecutive flocks on the same farm can be studied with longitudinal observational studies on farms (Huijbers et al., 2016; Dame-Korevaar et al., 2017) as by experimental studies (Ceccarelli et al., 2017). Transmission within and between flocks could be quantified using transmission experiments under controlled circumstances (Dame-Korevaar et al., unpublished data). In these experiments also possible interventions to reduce or prevent transmission could be tested (Ceccarelli et al., 2017).

Contamination of the environment surrounding farms can lead to indirect transmission between farms, but also between houses and subsequent flocks. Several articles report the presence of ESBL/pAmpC producing bacteria in litter, air, dust (Friese et al., 2013; Laube et al., 2013, 2014; Blaak et al., 2014, 2015; Sola-Gines et al., 2015; Daehre et al., 2017), but also in insects (Zurek and Ghosh, 2014; Smith et al., 2017) and in wildlife (Oluduro, 2012; Nhung et al., 2015; Stedt et al., 2015; Schaufler et al., 2016; Wang et al., 2017). However, the magnitude of this transmission route has not been quantified. Epidemiological and environmental studies can indicate associations between risk factors and contamination of farms or the environment, but quantification of environmental transmission is extremely difficult, if not impossible, and requires large amounts of longitudinal data. Studies from different regions suggest different transmission routes, transmission via the environment was mainly suggested based on data originating from non-European regions. Possibly this is related to differences in structure or management in poultry production between regions.

Observational studies in which the genetic similarity between isolates is used to study associations or possible transmission routes, often include only a small number or a selection of isolates and a complete view on different resistant genes/plasmids present in the animal or environment is lacking. This limits the insight in possible transmission routes. Also conclusions based on animal products or slaughterhouse samples should be interpreted with caution. Sampling in slaughterhouses or animal products, such as meat and eggs, are likely to be influenced by cross contamination during processing and handling (Cohen Stuart et al., 2012; Mollenkopf et al., 2014). These samples determine the exposure of humans, rather than represent an insight in the contamination of the production pyramid.

This review on different routes of transmission of ESBL/pAmpC producing bacteria in the broiler production pyramid shows scarce to no causal evidence of transmission along these routes and a lack of quantitative data. Therefore the relative contribution or magnitude of transmission via these routes cannot be quantified. This is a major gap in the knowledge on the transmission of ESBL/pAmpC producing bacteria in the poultry production chain and hampers the design of optimal intervention strategies.

6. Recommendations

There is a need for studies aiming to determine the existence, and quantify the magnitude of transmission via the four hypothesised routes of ESBL/pAmpC producing bacteria in the broiler production pyramid. Accurate detection of ESBL/pAmpC producing bacteria and typing of genes and plasmids using standardised methods is needed, especially because of the high level of heterogeneity in genes, plasmids and strains. This will help to compare occurrences within and between farms and countries and determine the extent to which resistant bacteria are transmitted through the production chain. High-resolution typing techniques, such as whole genome sequencing (WGS), can be used to study transmission routes, however even with these high-

resolution typing techniques there is a need for standardised methods to conclude on and show the importance of transmission routes. With information on the contribution of different transmission routes to the occurrence of ESBL/pAmpC producing bacteria in the production pyramid, interventions with the highest impact could be identified.

Conflicts of interest

None.

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Appendix 1

Complete search terms, including synonyms

Search term ‘poultry’ was defined in Pubmed as: ("Birds"[Mesh]) OR (poultry[tiab]) OR (broiler[tiab]) OR (broilers[tiab]) OR (laying hen[tiab]) OR (laying hens[tiab]) OR (farm[tiab]) OR (farms[tiab]) OR (breeder[tiab]) OR (parent stock[tiab]) OR (flock[tiab]) OR (chicken[tiab]) and in CAB Abstracts as: exp birds/ or exp poultry/ or exp broilers/ or exp hens/ or exp farms/ or breeder.ti. or breeder.ab. or parent stock.ti. or parent stock.ab. or exp flocks/ or exp fowls/ or chicken.ti. or chicken.ab.

Search term ‘ESBL’ was defined in Pubmed as: ("beta-Lactamases"[Mesh]) OR ("AmpC beta-lactamases"[Supplementary Concept]) OR (beta lactamase[tiab]) OR (beta-lactamase[tiab]) OR (beta lactamases[tiab]) OR (ampC[tiab]) OR (ampC beta lactamase[tiab]) OR (beta lactamase ampC[tiab]) OR (esbl[tiab]) OR (extended spectrum beta lactamase[tiab]) OR (resistance[ti]) OR (resistant[ti]) OR (plasmid[tiab]) OR (CMY[tiab]) OR (CTX[tiab]) OR (TEM[tiab]) OR (SHV[tiab]) OR (lactamase[tiab]) and in CAB Abstracts as: exp beta-lactamase/ or beta lactamase.ti. or beta lactamase.ab. or ampc.ti. or ampc.ab. or esbl.ti. or esbl.ab. or exp extended spectrum beta-lactamase/ or exp drug resistance/ or exp plasmids/ or cmy.ti. or cmy.ab. or tem.ti. or tem.ab. or ctx.ti. or ctx.ab. or shv.ti. or shv.ab. or lactamase.ti. or lactamase.ab. or resistance.ti. or resistant.ti. or plasmid.ti. or plasmid.ab.

Search term ‘spread’ was defined in Pubmed as: ("Disease Vectors"[Mesh]) OR (disease vectors[tiab]) OR (insect vectors[tiab]) OR (vectors[tiab]) OR (Route[tiab]) OR (Mechanism[tiab]) OR (mechanisms[tiab]) OR (Pathway[tiab]) OR ("Basic Reproduction Number"[Mesh]) OR (basic reproduction number[tiab]) OR (basic reproductive rate[tiab]) OR (basic reproductive ratio[tiab]) OR (R0[tiab]) OR (epidemic growth rate[tiab]) OR ("Infectious Disease Incubation Period"[Mesh]) OR (incubation period[tiab]) OR (generation time[tiab]) OR (transmission rate[tiab]) OR (transmission ratio[tiab]) OR (infection rate[tiab]) OR ("Disease Transmission, Infectious"[Mesh]) OR (transmission) OR (infection transmission[tiab]) OR [transmission infection[tiab]) OR (infectious disease transmission[tiab]) OR (transmission infectious disease[tiab]) OR (communicable disease[tiab]) OR (disease communicable[tiab]) OR (pathogen transmission[tiab]) OR (horizontal transmission[tiab]) OR (vertical transmission[tiab]) OR (horizontal[tiab]) OR (vertical[tiab]) OR (Spread[tiab]) OR (Introduction) OR (Dynamics[tiab]) OR (Transfer[tiab]) OR ("Disease Outbreaks"[Mesh]) OR (disease outbreak[tiab]) OR (disease outbreaks[tiab]) OR (outbreak[tiab]) OR (epidemic[tiab]) OR ("Endemic Diseases"[Mesh]) OR (endemic disease[tiab]) OR (endemic

[tiab]) OR ("Incidence"[Mesh]) OR (incidence[tiab]) OR (occurrence[tiab]) OR (prevalence[tiab]) OR (dissemination[tiab]) and in CAB Abstracts as: exp disease vectors/ or vector.ti. or vector.ab. or route.ti. or route.ab. or mechanism.ti. or mechanism.ab. or mechanisms.ti. or mechanisms.ab. or pathway.ti. or pathway.ab. or R0.ti. or R0.ab. or reproduction number.ti. or reproduction number.ab. or reproductive rate.ti. or reproductive rate.ab. or reproductive ratio.ti. or reproductive ratio.ab. or epidemic growth.ti. or epidemic growth.ab. or exp pre-patent period/ or generation time.ti. or generation time.ab. or transmission.mp. or exp disease transmission/ or exp infectious diseases/ or exp disease distribution/ or vertical.ti. or vertical.ab. or horizontal.ti. or horizontal.ab. or spread.ti. or spread.ab. or introduction.mp. or dynamics.ti. or dynamics.ab. or exp transfer/ or exp outbreaks/ or endemic.ti. or endemic.ab. or exp disease incidence/ or occurrence.ti. or occurrence.ab. or prevalence.ti. or prevalence.ab. or dissemination.ti. or dissemination.ab.

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