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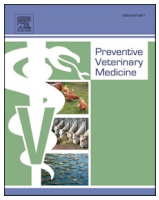

Transmission rates of veterinary and clinically important antibiotic resistant *Escherichia coli*: A meta- ANALYSIS

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ABSTRACT

The transmission rate per hour between hosts is a key parameter for simulating transmission dynamics of antibiotic-resistant bacteria, and might differ for antibiotic resistance genes, animal species, and antibiotic usage. We conducted a Bayesian meta-analysis of resistant *Escherichia coli (E. coli)* transmission in broilers and piglets to obtain insight in factors determining the transmission rate, infectious period, and reproduction ratio. We included ^{bla}CTX-M-1, ^{bla}CTX-M-2, ^{bla}OXA-162, *catA1, mcr-1,* and fluoroquinolone resistant *E. coli*. The Maximum a Posteriori (MAP) transmission rate in broilers without antibiotic treatment ranged from $0.4 \bullet 10^{-3}$ to $2.5 \bullet 10^{-3}$ depending on type of broiler (SPF vs conventional) and inoculation strains. For piglets, the MAP in groups without antibiotic treatment were between $0.7 \bullet 10^{-3}$ and $0.8 \bullet 10^{-3}$, increasing to $0.9 \bullet 10^{-3}$ in the group with antibiotic treatment. In groups without antibiotic treatment, the transmission rate of resistant *E. coli* in broilers was almost twice the transmission rate in piglets. Amoxicillin increased the transmission rate of *E. coli* carrying $bla_{\text{CTX-M-2}}$ by three-fold. The MAP infectious period of resistant *E. coli* in piglets with and without antibiotics is between 971 and 1065 hours (40 – 43 days). The MAP infectious period of resistant *E. coli* in broiler without antibiotics is between 475 and 2306 hours (20 – 96 days). The MAP infectious period of resistant *E. coli* in broiler with antibiotics is between 2702 and 3462 hours (113 – 144 days) which means a lifelong colonization. The MAP basic reproduction ratio in piglets of infection with resistant *E. coli* when using antibiotics is 27.70, which is higher than MAP in piglets without antibiotics between 15.65 and 18.19. The MAP basic reproduction ratio in broilers ranges between 3.46 and 92.38. We consider three possible explanations for our finding that in the absence of antibiotics the transmission rate is higher among broilers than among piglets: i) due to the gut microbiome of animals, ii) fitness costs of bacteria, and iii) differences in experimental set-up between the studies. Regarding infectious period and reproduction ratio, the effect of the resistance gene, antibiotic treatment, and animal species are inconclusive due to limited data.

1. Introduction

Transmission dynamics of antibiotic-resistant bacteria between livestock hosts are widely unknown despite the damaging impact of therapeutic failure due to antibiotic resistance in all animal species including humans (Alekshun and Levy, 2007). Cases of resistant bacteria against important last resort antibiotics such as carbapenem-resistant *E. coli* (CPE) have been occurring worldwide in livestock since 2010 (Köck et al., 2018). However up to now, CPE has not spread as extensively among livestock as extended spectrum beta-lactamase *E. coli* (ESBL) (Dahms et al., 2015).

Simulation modelling is a helpful tool to assess antibiotic resistant bacteria transmission dynamics and to evaluate intervention programs. While transmission simulations have traditionally been instrumental in comprehending the spread of infectious diseases within populations (Keeling and Rohani, 2008), their utility extends to the domain of

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antibiotic-resistant bacteria dynamics. Numerous studies have utilized simulation method to detangle the intricacies of resistant bacteria dissemination and persistence within livestock populations, thereby providing essential insights for bolstering surveillance efforts (Lanzas et al., 2011; Sorenson et al., 2017; Schulz et al., 2018). With modeling, we can simulate transmission dynamics that would otherwise be difficult to study in real-world situations due to economical and ethical constraints. Still, these simulations require a wide range of parameters, including the transmission rate. The accurate determination of the transmission rate (β) hold great importantance, as it significantly determines the model's outcomes and subsequent predictions (Kirkeby et al., 2017). Furthermore, transmission rate (β) is essential for the calculation of another vital parameter -the basic reproduction ratio (R_0). The basic reproduction ratio (R_0) is a vital parameter in epidemiology due to its role in predicting the number of new infections originating from an infectious animal during its period of infectivity. Following the introduction of antibiotic-resistant bacteria, R_0 is instrumental in gauging whether the bacteria will succeed in invading the susceptible population (Keeling and Rohani, 2008). A successful invasion becomes feasible when R_0 exceeds the threshold of 1. R_0 is calculated from the infectious period and the transmission rate, where the infectious period is the length of time that individual animal had been infectious until it returned to uncolonized state.

Transmission rates and infectious periods are most precisely estimated from transmission experiments in which animals are inoculated and the infection is allowed to spread to susceptible contact animals. To calculate the transmission rate, the infection status of individual animals is tracked over time. However, transmission experiments are restricted in size, treatment groups, housing and management conditions and limited sampling times due to costs (labor intensive), and ethical reasons (Hu et al., 2017). These restrictions often result in censored data for the infectious period because the moment that animal return to uncolonized state is beyond the end of experiment (Turkson et al., 2021). Consequently, there are no transmission experiments for resistant *E. coli* that have observed the full infectious period or that test multiple relevant factors such as antibiotic treatment, resistance gene, and animal species. To quantify the impact of antibiotic treatment, resistance gene, and animal species on the transmission rate of resistant *E. coli*, we conducted Bayesian meta-analysis of available transmission experiments.

Through the combination of multiple studies and incorporation of prior knowledge into the analysis, Bayesian meta-analysis can enhance the precision of the estimations of transmission rates and infectious period obtained from longitudinal experimental studies. The Bayesian hierarchical method, although well-established in various fields, is relatively uncommon in the veterinary domain (Gelman and Hill, 2006). However, its adoption here proves invaluable. The probabilistic prediction produced by this method is informative of both the data and the model, providing a more accurate representation of the uncertainty surrounding the estimations (McElreath, 2020). Meta-analysis increases sampling power by joining small scale studies with partial pooling, while penalizing against overfitting by using regularizing priors (McElreath, 2020). Bayesian inference is flexible and intuitive due to its adjustable prior and likelihood components (McElreath, 2020). Also, Bayesian inference produces a prediction in the form of a posterior distribution which is more informative of the model and data than a confidence interval (Gelman et al., 2021; Hiura et al., 2021; Vilares and Kording, 2011). The posterior distribution reflects the variability of the data, likelihood model and prior information while the confidence interval assumes that the entire range of the confidence interval of a uniform distribution has equal opportunity to be the true value.

Here, Bayesian meta-analysis was employed to infer transmission rates and infectious periods of *E. coli* with different resistance genes in both piglets and broilers from transmission experiments. Environmental transmission was assumed, because bacteria such as *E. coli* are transferred between animal hosts through the faecal-oral route and can survive in the farm environment as long as 30 days (Lister and Barrow, 2008; van Bunnik et al., 2014; van Elsas et al., 2011). We aimed to identify factors determining the transmission rate and whether these resistant bacteria will successfully invade livestock populations after their introduction.

2. Materials and methods

A systematic review was conducted following the PRISMA protocol (PRISMA, 2020). Transmission events and infectious periods were extracted from longitudinal experimental transmission studies. The raw individual animal data were extracted from all studies in order to conduct the Meta-analysis of individual participant data (Riley et al., 2019). Transmission events were fitted to an SIS model with environmental transmission (Gerhards et al., 2022) using a Bayesian hierarchical inference model to obtain transmission rates. Infectious periods were fitted with non-parametric survival analysis using a Bayesian hierarchical inference.

2.1. Systematic literature review and data extraction

This Bayesian meta-analysis was conducted following the PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2020 checklist. The extensive protocol is included in Supplementary I.

First author (ND) performed the literature search in 2022. Pubmed and Google Scholar were the online database in which the search are performed. The search strategy encompassed a combination of three distinct categories of search terms: those related to meat-producing livestock, antimicrobial-resistant bacteria, and longitudinal data. The initial search results were carefully screened to remove duplicate records. Subsequently, a set of specific selection criteria were applied to identify relevant studies, which included: 1) inclusion of longitudinal data 2) presence of distinct contact and challenge animals, with the challenge animals being inoculated with non-pathogenic resistant bacteria 3) restriction to studies involving non-pathogenic resistant bacteria and meat-producing animal as the host species. Throughout this process, we implemented a hierarchical screening approach. We began by thoroughly reviewing the titles of the identified records to identify relevant studies. Next, we proceeded to screen the abstracts of the remaining records, further narrowing down the selection. Finally, the smallest subset of records underwent a comprehensive review, with the entire manuscripts being scanned with the selection criteria. Furthermore, the selected records undergo a Risk of Bias assessment to evaluate and minimize potential biases arising from selection and analysis during the study's design, conduct, reporting, and analysis phases (Higgins et al., 2011).

3. Outcome

The excreting status (positive or negative for resistance markers) of individual animals was extracted at each sampling time point. For each individual animal, we extracted the pen information, the inoculation strain, any antibiotic treatments (yes/no), and the inoculation status (inoculated animal versus contact animal). Contact animals were classified as susceptible animals and could become cases, subsequently becoming infectious animals, whereas the inoculated animals could only become infectious but were not counted as cases.

The number of hours that an animal (contact and inoculated) excreted *E. coli* carrying resistance was extracted as an input for the infectious period (D). Resistance is defined as either resistance gene or phenotypic resistance. We assumed that all individuals would stop excreting the *E. coli* carrying resistance at the end of their infectious period (return to uncolonized state). Hence, to extract the infectious period, we counted hours from the first sampling time point that an animal is excreting (positive for resistance marker) until the first sampling time point that an animal stop excreting (negative for resistance

marker). Only animals that exhibit at least two consecutive negative samples were considered to have undergone loss of colonization and potentially became colonized again. Animals that showed a single negative sample following a positive result, and return to an uncolonized state, were adjusted by reclassifying that negative sample as positive. Additionally, We run the analysis in the dataset that did not have reclassification of single negative sample. The result of the analysis is included in Supplementary material V. Animals that return to uncolonized state and became infectious again could have more than one infectious period.

If the time that an animal's return to an uncolonized state is censored, indicating that the animal continues to excrete *E. coli* carrying resistance genes until the end of the experiment, we calculate the infectious period by measuring the time from the initial sampling time point, when the animal starts excreting (positive for the resistance marker) until the last observed sampling time point. In this context, we assume that the period of time during which an animal returns to an uncolonized state extends beyond the actual end of the experiment. This assumption about the time for an animal to return to an uncolonized state follows the gamma distribution, accounting for variations in return dynamics among the subjects.

4. Data synthesis

Before we apply the Bayesian hierarchical model, we adopted the Meta-analysis of Individual Participant Data technique to extract individual animal outcomes, such as excretion status across time points. These data were subsequently organized into pen clusters, facilitating analysis. Subsequently, the Bayesian hierarchical model was applied, incorporating the complete individual dataset, and treating pen clusters as random effects.

4.1. Transmission model

We used an susceptible-infectious-susceptible (SIS) transmission model with environmental transmission (Gerhards et al., 2022). Within the same pen, susceptible animals (S_t) may become colonized (I_t) through infectious material deposited in the environment and can subsequently return to uncolonized state and become susceptible again. Infectious material deposited in the environment determines the instantaneous environmental hazard (E_t). The excreted bacteria and thus the hazard will decay with a constant rate (δ) per hour and the hazard due to viable bacteria results in colonization with rate (β) per hour of susceptible animals (Dankittipong et al., 2023). Because we do not know the exact number of bacteria excreted by a broiler chicken or pig, we scaled this excretion into one unit of excreted bacteria by one animal per hour (Gerhards et al., 2022) using scaling factor $\omega = \frac{\delta^2}{\delta + e^{-\delta} - 1}$. The R_0 in this model is for an average infectious period (D): $R_0 = \frac{\beta\omega}{\delta} D = \beta \frac{\delta}{\delta + e^{-\delta} - 1} D$. (Gerhards et al., 2022).

4.2. Bayesian hierarchical inference for transmission rate per hour

We applied Bayesian inference for the parameters of the transmission model for each pen i. The transmission rate (hour^{-1}) parameter of each pen (β_i) was calculated in two steps. The number of new cases during a time interval is taken to be binomially distributed with logit link function comprised of the number of trials equalling the number of susceptible animals in pen(S_i) and the probability of transmission (p_i). The probability of transmission during an interval is calculated given a pen-specific transmission rate per hour (β_i). In the log likelihood function, the log transmission rate per hour is modeled with the mean log population transmission rate per hour ($\log(\overline{\beta})$) and the variation of transmission rate between pens (z_i). The exponent of the log transmission rate per hour is then multiplied by the instantaneous hazard of colonization (E_t). This hazard is obtained by scaling the excretion to the total amount of bacteria excreted by an animal per unit of time, (Gerhards et al., 2022). The decay rate per hour of *E. coli* carrying resistance genes in environment could not be estimated from our data. Therefore, we reviewed literature for estimated decay rates of *E. coli* in environment and applied these to the model (Supplementary table S1). We used weighted Akaike information criterion (WAIC) and the number of divergences to select the decay rate thus based on the model's goodness-of-fit to the observed data while considering its complexity. WAIC is particularly useful for comparing models with different parameters, while divergences can help diagnose issues with the Markov chain Monte Carlo (MCMC) algorithm's convergence and posterior estimates.

A weakly informative prior for the log mean transmission rate per hour ($\log(\overline{\beta})$) follows a normal distribution with mean of −10 and standard deviation of 10. The prior for variation of transmission rates per hour between pens (z_i) follows a normal distribution with mean of 0 and standard deviation of 1 (Supplementary table S2). We used a fixed decay rate per hour (δ) of 0.13 hour^{-1}.

The posterior distribution of the transmission rate per hour in each pen (β_i) was extracted and, for comparisons, grouped and averaged by the resistance gene in the inoculation, host species and antibiotic treatment. The posterior distributions are either presented in figures or by the Maximum A Posteriori (MAP) and 97% Highest Probability Density Interval (97% HDPI).

To compare two transmission rates per hour for different factors such as animal species, we determined the entire posterior distribution of ratios between the transmission rates per hour of two factors by dividing the rates per hour in each sample of the posterior distribution. A ratio of one means the transmission rates per hour are equal for the two factors. Furthermore, we determined whether the transmission for one factor was lower than the other by calculating the probability that the ratio is lesser than one (P<1) by summing iterations that resulted in ratio lessor than one and dividing the sum with the total number of iterations.

4.3. Bayesian parametric survival analysis for infectious period

Bayesian parametric survival analysis was used to quantify the infectious period (D) in each pen (i). The infectious period (D) refers to the duration (in hours) during which an animal is colonized before returning to an uncolonized state and becoming susceptible to the disease. We assumed that the observed infectious periods of all animals in each pen (D_{obs_i}) follows a gamma distribution with the pen-specific shape (a_i) and a rate parameter which is same at each animal (b), where the shape parameter is normally distributed with the mean population shape ($\overline{a}$) and variation of the shape for each pen (σ_i).For censored values of the infectious period, we characterized the distribution of the infectious period to be a cumulative gamma distribution of shape (a_i) and rate (b_i).

Prior information of the infectious period was obtained from studies of *E. coli* O157 in one-day-old specific-pathogen free (SPF) layer chickens and extended-spectrum cephalosporin-resistant *E. coli* in commercial piglets and fattening pigs (Moor et al., 2021;Ragione et al., 2005). In broiler, a regularizing weakly informative prior for the mean population shape ($\overline{a}$) follows a normal distribution with mean of 0 and standard deviation of 1. The variation of the shape of gamma from each pen (σ_i)follows an exponential distribution with the rate of 1. The rate parameter (b_i) follows a standard normal distribution with mean of 0 and standard deviation of 1. In piglets, a regularizing weakly informative prior for the mean population shape ($\overline{a}$) follows a normal distribution with mean of 0 and standard deviation of 2 and the same prior for other parameters. The entire posterior distributions of shape in each pen (a_i) and rate (b_i) were extracted. The estimated mean infectious period of each pen (D_i) was calculated by dividing shape parameter in each pen (a_i) with rate (b_i).

4.4. Bayesian hierarchical inference for reproduction ratio

The posterior distribution for the basic reproduction ratio of each pen (R_{0_i}) is derived from each sample of the posterior distribution of the transmission rate per hour in each pen (β_i) combined by each sample from the posterior distribution of the infectious period of each pen (D_i).

$$R_{0_i} = (\beta_i \otimes D_i)\frac{\delta}{\delta + e^{-\delta} - 1}$$

To illustrate, we take 20,000 samples from the posterior distribution of transmission rate per hour in each pen. We then perform a multiplication process where each sample from this distribution is paired with the corresponding sample from the posterior distribution of the mean infectious period of each pen (D_i). This element-by-element multiplication ensures that the posterior distribution of R_{0_i} encompass all potential combinations of transmission rates per hour and infectious periods (hours), thereby accurately accounting for their relationship. Consequently, we obtain the posterior distribution of the basic reproduction ratio of each pen (R_{0_i}) resulting in a total of 4×10^8 derived from $20,000^2$ samples. In the total, we obtained 6.4×10^{10} estimated for the basic reproduction ratio across 40 pens.

Similary to transmission rate per hour, reproductive ratio (R_{0_i}) and mean infectious period of each pen (D_i) were grouped based on the resistance gene in the inoculation, the host species and the antibiotic treatment. We extracted and presented the average transmission rate per hour from multiple pens with the same variables and presented as Maximum A Posteriori (MAP) and 97% Highest Probability Density Interval (97% HDPI).

All analysis were done in R version 4.1.2 (R development Core Team, 2022) and Bayesian inference was done in RStan 2.21.5 (Stan Development Team, n.d.) with 14 tree depth, 0.99 acceptance rate and 4 chains, each chain with 10,000 iterations. 5000 iterations from each chain were excluded as warm-up samples resulting in a total of 20,000 iterations from 4 chains. The codes will be provided as supplementary information 4.

5. Results

5.1. Literature search result

The initial search across the Pubmed and Google Scholar databases was conducted in June 2022 and yielded a total of 2055 papers. Following a review, 3 duplicate papers were identified and subsequently excluded from the dataset. Among the remaining entries, 21 publications were found to be pertinent to the topic of resistant bacteria in livestock. After a screening process, 5 publications met the criteria for inclusion in the final analysis.

5.2. Risk of bias

Cochrane's risk of bias assessment was applied to all included studies (Higgins et al., 2011). Overall, the studies share a similar experimental

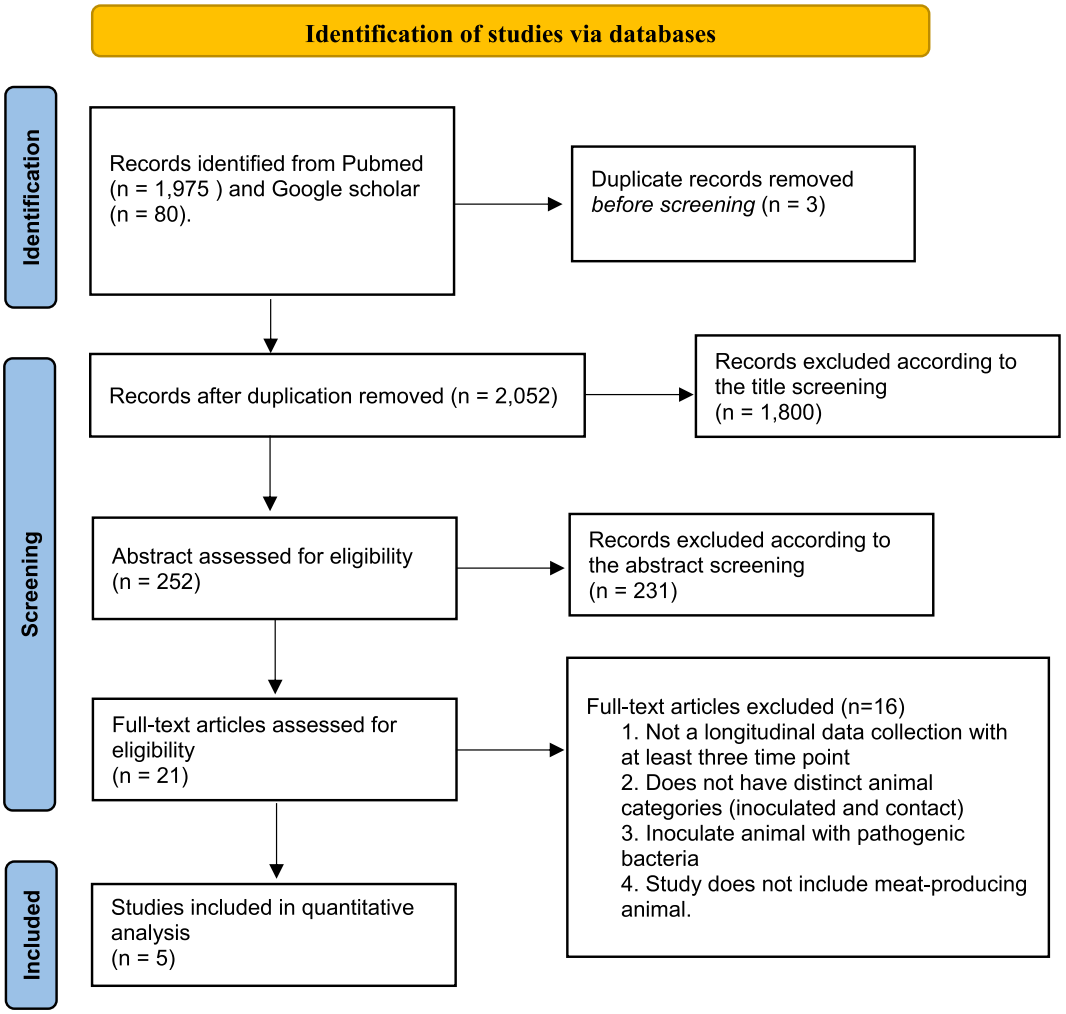

Fig. 1. PRISMA protocol for systematic literature review to collect longitudinal data of resistance genes transmission between meat-producing animals.

design, phenotypic resistance analysis, and individual resistance reporting. Consequently, the risk of biases in all studies is low, although there are minor concerns related to the absence of blinding the experimenters to the treatment and the lack of a pre-specified experiment plan in the records. We consider these concerns negligible since the outcomes, including resistance and susceptible status of individual animals at each sampling time point, are objectively determined by the EU protocol (ECDC, 2023).Fig. 1

5.3. Transmission experiment data

We extracted three longitudinal experimental studies in broilers, with in total 170 one-day old conventional broilers and 36 five-day old SPF broilers. Cloacal samples were enriched overnight and then inoculated onto selective MacConkey plates supplemented with antibiotics of interest. In broilers, the concentration of antibiotics and antibiotics of choice were consistent across all studies, comprising 1 mg/L of cefotamine, 0.5 mg/L of ertapenem, or 64 mg/L chloramphenicol. Dame-Korevaar et al. (2018) investigated the transmission rate of *E. coli* carrying $bla_{\text{CTX-M-1}}$ resistance gene with $0.5\bullet10^{1}$ and $0.5\bullet10^{2}$ cfu/animal inoculation doses in one-day old conventional broilers (Table 1). Ceccarelli et al. (2017) inoculated five-day old SPF broilers with *E. coli* carrying $bla_{\text{CTX-M-1}}$ genes with doses of $0.5\bullet10^{6}$ and $0.5\bullet10^{8}$ cfu/animal. Dankittipong et al. (2023) evaluated the transmission of *E. coli* carrying $bla_{\text{OXA-162}}$, *E. coli* carrying $bla_{\text{CTX-M-2}}$, and *E. coli* carrying *catA1*, all of which were inoculated at $0.5\bullet10^{3}$ cfu/animal in five-day old conventional broilers. In this study, half of the animals received amoxicillin treatment (20 mg/kg of broiler) for five days starting three days before inoculation (Dankittipong et al., 2023). Thus, half of the animal were inoculated during antibiotic treatment In all three studies, the inoculated and susceptible chicks acquired *E. coli* carrying resistance genes, except for one pen of conventional broilers that were inoculated with $0.5\bullet10^{1}$ cfu/animal of *E. coli* carrying $bla_{\text{CTX-M-1}}$ in Dame-Korevaar et al. (2018). In this pen none of the inoculated animals started shedding and thus the transmission rates cannot be estimated. From five studies, we extracted a total of 204 infectious periods from 191 broilers, 13 of which returned to uncolonized state and were recolonizied.

For piglets, we extracted three longitudinal experimental studies with in total 101 SPF piglets of seven to eight weeks old. Rectals samples from piglets were enriched overnight and cultured on Chromagar plates with relevant antibiotic supplements. Antibiotic concentrations varied slightly between studies. For the *mcr-1* resistance study by Mourand et al. (2018), (2019), plates were supplemented with 250 mg/L rifampicin, while the fluoroquinolone resistant study by Andraud et al. (2011) employed 0.5 mg/L ciprofloxacin. Two experiments were conducted by Mourand et al. (2018), (2019) to test transmission rate of *E. coli* carrying *mcr-1* resistance genes with $2.5\bullet10^{5}$ and $2.5\bullet10^{8}$ cfu/animal inoculation doses. In the study of Mourand et al. (2019), colistin was administered at a dosage of 12,500 IU/kg (which is 4 mg/kg) live weight for three days. This administration occurred through two separate protocols within two distinct groups of piglets. In the first group, colistin treatment was initiated seven days before the planned inoculation. In contrast, the second group received colistin administration just one hour before the planned inoculation on day 7. Subsequently on day 7, piglets of eight weeks old from both groups were inoculated with $2.5\bullet10^{8}$ cfu/animal inoculation doses. The two pens, previously treated with colistin seven days before inoculation, were excluded from the analysis because these results could not be compared between piglets and broilers (i.e.,

Table 1
Transmission rate per hour from different host species, status, mode of transmission, resistance, and antibiotic treatment. MAP denotes Maximum a priori and 97% HPDI denotes 97% higest posterior density distribution. Resistance included the.

Species	Status	Resistance	Antibiotic	Number of animals	Inoculated dose (cfu/animal)	MAP (h^{-1})	97% HPDI	Reference
Broilers	Specific pathogen free animals	$bla_{\text{CTX-M-1}}$	No	20	$0.5\bullet10^{6}$	$2.5\bullet10^{-3}$	$1.2\bullet10^{-3}$, $9.4\bullet10^{-3}$	Ceccarelli et al., (2017)
		$bla_{\text{CTX-M-1}}$	No	16	$0.5\bullet10^{8}$	$1.6\bullet10^{-3}$	$0.9\bullet10^{-3}$, $3.3\bullet10^{-3}$	Ceccarelli et al., (2017)
	Conventional	$bla_{\text{CTX-M-1}}$	No	10	$0.5\bullet10^{1}$	$0.4\bullet10^{-3}$	$0.1\bullet10^{-3}$, $2.4\bullet10^{-3}$	Dame-Korevaar et al., (2020)
		$bla_{\text{CTX-M-1}}$	No	30	$0.5\bullet10^{2}$	$2.2\bullet10^{-3}$	$1.4\bullet10^{-3}$, $4.6\bullet10^{-3}$	Dame-Korevaar et al., (2020)
		$bla_{\text{CTX-M-2}}$	No	20	$0.5\bullet10^{3}$	$0.7\bullet10^{-3}$	$0.4\bullet10^{-3}$, $1.1\bullet10^{-3}$	Dankittipong et al., (2023)
		$bla_{\text{OXA-162}}$	No	20	$0.5\bullet10^{3}$	$0.4\bullet10^{-3}$	$0.3\bullet10^{-3}$, $0.8\bullet10^{-3}$	Dankittipong et al., (2023)
		catA1	No	20	$0.5\bullet10^{3}$	$1.0\bullet10^{-3}$	$0.6\bullet10^{-3}$, $1.6\bullet10^{-3}$	Dankittipong et al., (2023)
		$bla_{\text{CTX-M-2}}$	Amoxicillin	20	$0.5\bullet10^{3}$	$2.6\bullet10^{-3}$	$1.4\bullet10^{-3}$, $4.3\bullet10^{-3}$	Dankittipong et al., (2023)
		$bla_{\text{OXA-162}}$	Amoxicillin	20	$0.5\bullet10^{3}$	$0.6\bullet10^{-3}$	$0.3\bullet10^{-3}$, $1.3\bullet10^{-3}$	Dankittipong et al., (2023)
		catA1	Amoxicillin	20	$0.5\bullet10^{3}$	$0.8\bullet10^{-3}$	$0.3\bullet10^{-3}$, $3.3\bullet10^{-3}$	Dankittipong et al., (2023)
Piglets	Specific pathogen free animals	*mcr-1*	No	10	$2.5-9\bullet10^{8}$	$0.8\bullet10^{-3}$	$0.5\bullet10^{-3}$, $1.4\bullet10^{-3}$	Mourand et al., (2019)
		Fluoroquinolone	No	51	$1.0\bullet10^{10}$	$0.7\bullet10^{-3}$	$0.5\bullet10^{-3}$, $1.1\bullet10^{-3}$	Andraud et al., (2011)
		mcr-1	Colistin	20	$2.5-9\bullet10^{8}$	$0.9\bullet10^{-3}$	$0.4\bullet10^{-3}$, $2.5\bullet10^{-3}$	Mourand et al., (2019)

inoculation during antibiotic treatment). In the study of Mourand et al. (2018), *E. coli* carrying *mcr-1* resistance genes with $2.5\bullet10^5$ and $2.5\bullet10^8$ cfu/animal inoculation doses were inoculated to seven-week old piglets. Two pens inoculated with $2.5\bullet10^5$ cfu/animal did not result in any shedding in the inoculated animals and thus were excluded from the analysis. Point-mutated fluoroquinolone resistant *E. coli* transmission between seven weeks old piglets was studied by Andraud et al. (2011) with an inoculation dose of 10^{10} cfu/animal. All piglets in seven pens became colonized with *E. coli* carrying fluoroquinolone resistance. A total count of 81 piglets were obtained from three separate studies. Out of these, 18 piglets experienced a return to uncolonized state and recolonization. As a result, a cumulative total of 99 instances of infectious periods were considered for the estimation of the infectious period. Overall, 27 pens of broilers and 13 pens of piglets were included in the inference of transmission rate per hour.

5.4. Transmission rate of resistant bacteria within same host species

Overall transmission rates per hour of *E. coli* carrying resistance in piglets ranged from $0.4\bullet10^{-3}$ h^{-1} to $2.5\bullet10^{-3}$ h^{-1}, according to the lowest to highest value of 97% highest posterior density interval (97% HPDI). Among piglets, the highest Maximum a Posteriori (MAP) transmission rate ($0.9\bullet10^{-3}$ h^{-1}) is from *E. coli* carrying *mcr-1* in piglets treated with colistin. In the piglet group without antibiotic treatment, the MAP transmission rate of *E. coli* carrying fluoroquinolone resistance and *mcr-1* are $0.7\bullet10^{-3}$ h^{-1} and $0.8\bullet10^{-3}$ h^{-1} respectively.

In broilers, the transmission rates of *E. coli* carrying resistance genes ranged from $0.1\bullet10^{-3}$ h^{-1} to $9.4\bullet10^{-3}$ h^{-1}(97% HPDI). The highest MAP transmission rate among *E. coli* carrying resistance genes in broilers without antibiotic treatment was observed for *E. coli* carrying $bla_{\text{CTX-M-1}}$ ($2.5\bullet10^{-3}$ h^{-1}). In the broiler group with antibiotic treatment, *E. coli* carrying $bla_{\text{CTX-M-2}}$ had the highest MAP transmission rate ($2.6\bullet10^{-3}$ h^{-1}).

Furthermore, the studies with *E. coli* carrying $bla_{\text{CTX-M-1}}$ involved multiple inoculation doses ranging from $0.5\bullet10^1$ cfu/animal to $0.5\bullet10^8$ cfu/animal. The low inoculation dose of $0.5\bullet10^1$ cfu/animal resulted in a lower transmission rate per hour compared to the transmission rate per hour of other inoculation dosages. This lower dosage even prevented transmission in one pen. Despite the use of this lower inoculation dosage of *E. coli* carrying $bla_{\text{CTX-M-1}}$, the transmission rate per hour surpasses the rates observed for the other resistance genes at higher dosages under no antibiotic treatment (Table 1)

5.5. Comparing the transmission rate between groups with and without antibiotic treatment

Amoxicillin accelerated the transmission of *E. coli* carrying $bla_{\text{CTX-M-2}}$ resistance genes but had no effect on the transmission rate per hour of the other resistance genes. Fig. 2 shows the 3.34 fold higher transmission rate per hour for *E. coli* carrying $bla_{\text{CTX-M-2}}$ in the group treated with amoxicillin than the untreated group. Amoxicillin and colistin seemed to slightly increase the transmission rate per hour of *E. coli* carrying $bla_{\text{OXA-162}}$ and *E. coli* carrying *mcr-1*. However, the ratio range of 0.42–3.55 (97% HPDI) cannot decisively establish the influence of antibiotics on the transmission of *E. coli* carrying $bla_{\text{OXA-162}}$ and *E. coli* carrying *mcr-1*. This range encompasses values from 0.42 (suggesting no significant effect from colistin and amoxicillin) up to 3.55 (indicating a potential tripling of the transmission rate per hour under colistin and amoxicillin treatment). For *E. coli* carrying *catA1* genes, our observations indicate a generally reduced transmission rate per hour when subjected to amoxicillin treatment. However, this finding was even less conclusive due to the fact that nearly half (0.46) of the posterior distribution indicates lower transmission rates per hour(Fig. 2).

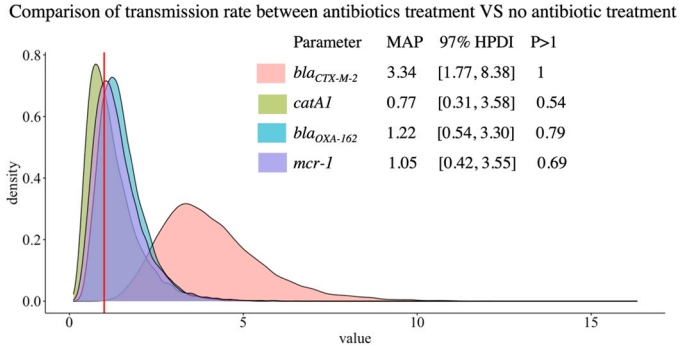

Fig. 2. Posterior distributions of the ratio of transmission between antibiotic treatments (no antibiotic treatment vs. with antibiotic treatment) for different resistance genes in broilers and piglets.

5.6. Comparing the transmission rate in broilers versus piglets

Without antibiotics, the transmission rate per hour between broilers was higher (probability of 0.99) than between piglets, and this was on average two-fold higher. In contrast, under antibiotic treatment the same transmission rate per hour was found for piglets and broilers (Fig. 3).

5.7. Infectious period and reproduction ratio

The 97% HPDI of infectious periods of *E. coli* carrying resistance genes in broiler without antibiotic treatment are between 227 and 46,007 hours (9 – 1917 days) (Table 2). In the group with antibiotic treatment, the HPDI of infectious periods for *E. coli* carrying resistance genes in broiler are between 868 and 56,678 hours (36 – 2362 days) (Table 2). *E. coli* carrying $bla_{\text{OXA-162}}$ showed the highest MAP infectious period in broiler with antibiotic treatment, at 3462 hours (144 days), compared to the lowest MAP infectious period of 475 hours (20 days) without antibiotic treatment. Antibiotic treatment increased the infectious period of *E. coli* carrying $bla_{\text{OXA-162}}$ by 6-fold (Table 3). Antibiotic treatment seemed to increase the infectious period of *E. coli* carrying $bla_{\text{CTX-M-2}}$ although with 0.25 probability of no effect. The 97% HPDI of the infectious periods is extremely wide for most treatment groups in broilers due to the limited number of animals that stopped excreting the bacteria during the experiment.

According to Table 2, the 97% HPDI infectious period of *E. coli* carrying resistance genes in piglets without antibiotic treatment is between 617 and 4299 hours (26 – 145 days). In the group with antibiotic treatment, the HPDI infectious periods of *E. coli* carrying resistance genes in piglets was similar, ranging from 622 to 4694 hours (26 – 196 days) (Table 2). *E. coli* carrying fluoroquinolone resistance had the shortest MAP infectious period. The infectious period of *E. coli* carrying *mcr-1* was not affected by antibiotic treatment.

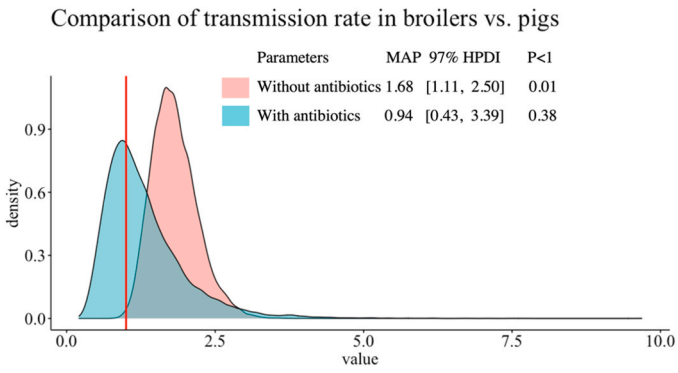

Fig. 3. Posterior distributions of transmission rate ratio of broilers and piglets when treated and not treated with antibiotics.

Table 2
Posterior distribution of infectious periods (hours) and reproduction ratio in different host species, resistance, and antibiotic treatment.

Species	Resistance	Antibiotics	Infectious period (in hours); MAP [97% HPDI]	Reproduction ratio; MAP [97% HPDI]
Broiler	$bla_{CTX\text{-}M\text{-}1}$		2306 [1329,46007]	92.38 [47,2049]
	$bla_{CTX\text{-}M\text{-}2}$		1096 [586,24905]	11.33 [5.4, 298]
	$bla_{OXA\text{-}162}$		475 [277,1254]	3.46 [1.7, 11.92]
	catA1		1157 [462,33248]	16.89 [7.64, 883]
	$bla_{CTX\text{-}M\text{-}2}$	Amoxicillin	2901 [950,55906]	74.80 [35,2560]
	$bla_{OXA\text{-}162}$	Amoxicillin	3462 [868,50724]	16.71 [7.2, 717]
	catA1	Amoxicillin	2702 [893,56678]	23.03 [10.4, 1270]
Piglet	*Fluoroquinolone resistance*		971 [617,3468]	15.65 [8.40, 115.31]
	mcr-1		1065 [687,4299]	18.19 [8.87, 206.98]
	mcr-1	Colistin	1043 [622,4694]	27.70 [9.06, 383.53]

The basic reproduction ratio (R_0) in broilers varies greatly between resistance and antibiotic treatments (Table 2). The 97% HPDI reproduction ratio in broiler is between 1.7 and 2560 depending on the resistance and treatment. In broilers, the MAP R_0 (i.e. the reproduction without antibiotic treatment) is highest with 92.38 for *E. coli* carrying $bla_{CTX\text{-}M\text{-}1}$. *E. coli* carrying $bla_{OXA\text{-}162}$ with 3.46, has the lowest MAP R_0 among the groups without antibiotic treatment. However, both values are well above the threshold value 1. Conversely, *E. coli* carrying $bla_{OXA\text{-}162}$ with antibiotic treatment has the highest MAP reproduction ratio among the group with antibiotic treatment. Antibiotic use increased the reproduction ratio of *E. coli* carrying $bla_{CTX\text{-}M\text{-}2}$ and *E. coli* carrying $bla_{OXA\text{-}162}$ by three-fold, but had inconclusive effect on the reproduction ratio of *E. coli* carrying *catA1* (Table 3).

The 97% HPDI R_0 of piglet is between 8.40 and 384. The 97% HPDI R_0 of all inoculations are overlapping. *E. coli* carrying fluoroquinolone resistance has with 15.65 the lowest MAP R_0. The effect of resistance genes and antibiotic treatment for piglets toward the R_0 is inconclusive, because of the large overlap in posterior distributions. The overall reproduction ratio in broilers without antibiotic treatment is two-fold of that of piglets without antibiotic treatment.

6. Discussion

In our study we found a rapid transmission of *E. coli* carrying $bla_{CTX\text{-}M\text{-}1}$ and $bla_{CTX\text{-}M\text{-}2}$ compared to strains with other resistance genes. Notably, we found that amoxicillin increases the transmission of $bla_{CTX\text{-}M\text{-}2}$ by three-fold. Furthermore, we predict that *E. coli* carrying resistance genes in broilers may have a wide range of infectious periods, potentially lasting a lifetime. Additionally, we observed that transmission of *E. coli* carrying resistance genes is faster between broilers than piglets in the absence of antibiotic treatment.

Our study indicates that in the absence of antibiotics the transmission rate of *E. coli* carrying resistance genes is higher among broilers than among piglets. We consider three possible explanations for this finding: the gut microbiome of animals, fitness costs of bacteria, and differences in experimental set-up between the studies.

First, the piglets were older than the broilers. The stability of the gut microbiome of piglets and broilers increases with the age of the animals (Guevarra et al., 2019; Ranjitkar et al., 2016). A stable gut microbiome has a preventive effect against resistant bacteria invasion (Lozupone et al., 2012; Sorbara and Pamer, 2019). Exogenous and potentially resistant bacteria will readily colonize an unstable gut microbiome (Kim et al., 2017; Rochegüe et al., 2021). Diverse bacteria species in a stable gut microbiome establish complex interactions to achieve homeostasis within the gut which results in a preventive effect against invasion of exogeneous bacteria (Awad et al., 2016; Lozupone et al., 2012; Rochegüe et al., 2021). In our meta-analysis, broilers were one to five day olds at the start of the experiment while piglets were at least seven weeks old. Young broilers of less than one week old typically have a volatile gut microbiome and are most vulnerable to *E. coli* colonization (Ranjitkar et al., 2016; Zhu and Joerger, 2003)(Chen et al., 2017; Guevarra et al., 2019; Zhou et al., 2021).

Secondly, specific resistance genes or the mobile elements with which these are associated could impose different fitness cost to *E. coli* thereby determining the transmission rate (Melnyk et al., 2015). Some genes are even associated with an improved fitness of bacteria without antibiotic treatement (Andersson, 2006; Borrell et al., 2013; Luo et al., 2005; Melnyk et al., 2015; Dionisio et al., 2005). Betalactamase producing genes (in our study $bla_{CTX\text{-}M\text{-}1}$ and $bla_{CTX\text{-}M\text{-}2}$) are known to rapidly colonize host populations and diversify worldwide due to their highly mobilized genetic characters which suggests low fitness cost of these genes for the *E. coli* bacteria (Cantón et al., 2012; Palmeira et al., 2020; Conway and Cohen., 2015). Transmission rates per hour of *E. coli* carrying $bla_{CTX\text{-}M\text{-}1}$ and $bla_{CTX\text{-}M\text{-}2}$ genes in broilers were highest in our meta-analysis (Table 1). This indicates low fitness cost of $bla_{CTX\text{-}M\text{-}1}$ and $bla_{CTX\text{-}M\text{-}2}$ genes incurred to *E. coli*. While direct transmission experiment data involving *E. coli* carrying $bla_{CTX\text{-}M\text{-}1}$ among piglets is lacking, it is important to consider the consistently high prevalence of $bla_{CTX\text{-}M\text{-}1}$ *E. coli* in Dutch pigs (MARAN, 2020). This prevalence of *E. coli* carrying $bla_{CTX\text{-}M\text{-}1}$ among pigs suggests the potential for rapid transmission of *E. coli* carrying $bla_{CTX\text{-}M\text{-}1}$ exists between piglets as well. This observation, highlighted in national surveillance (2020), raises the possibility that piglet-to-piglet transmission of *E. coli* carrying $bla_{CTX\text{-}M\text{-}1}$ could occur at an accelerated rate. Although we did not have transmission experiment data of *E. coli* carrying $bla_{CTX\text{-}M\text{-}1}$ between piglets, we expect that *E. coli* carrying $bla_{CTX\text{-}M\text{-}1}$ would have a fast transmission rate in piglets as well. This would be in line with consistently high detection of $bla_{CTX\text{-}M\text{-}1}$ *E. coli* in Dutch pigs (MARAN, 2020).

Thirdly, variation of experimental settings, specifically housing, affects transmissibility of bacteria from the environment to the animal. In this meta-analysis, piglets were all housed in pens in a stable. Piglets inoculated with *E. coli* carrying fluoroquinolone resistance were housed on a slatted floor. Slatted floors may reduce transmission rate as part of excreted feces contaminated with resistant bacteria is sieved through these floors (Andraud et al., 2011). Though the type of floor was not

Table 3
Posterior distribution of the ratio of infectious period between antibiotic treatments (no antibiotic treatment vs. with antibiotic treatment) for different resistance in broilers and piglets.

Species	Resistance	Antibiotics	Ratio of Infectious period; MAP [97% HPDI]	Ratio of Infectious period; P<1	Ratio of reproduction ratio; MAP [97% HPDI]	Ratio of Infectious period; P<1
Broiler	$bla_{CTX\text{-}M\text{-}2}$	Amoxicillin	2.18 [0.16, 27.49]	0.26	3.08 [0.74, 82.75]	0.04
	$bla_{OXA\text{-}162}$	Amoxicillin	7.28 [1.60, 102.9]	0	3.72 [1.7, 123.2]	0.01
	catA1	Amoxicillin	1.05 [0.14, 30.45]	0.23	0.39 [0.11, 23.12]	0.37
Piglet	*mcr-1*	Colistin	0.91 [0.33, 2.93]	0.51	0.52 [0.20, 11.16]	0.34

mentioned in Mourand et al. (2018) and, (2019), it is possible that their piglets were housed in a similar setting given both teams complied to same French regulation on animal welfare in experimentation (Mourand et al., 2019, 2018). This removal of feces through housing was not present in the experimental setting for broilers in isolators or pens without slatted floors (Ceccarelli et al., 2017; Dame-Korevaar et al., 2020) and could contribute to faster transmission rate between broilers than between piglets. Moreover, considering the distinction between SPF and conventional broiler chickens could further elucidate the observed transmission dynamics. The uncertainty highlighted by the wide-ranging probability distribution, resulting from evaluating the posterior distribution of transmission rate ratio of SPF broiler chickens and of conventional broiler chickens (ranging from 0.5 to 2.7), suggesting inconclusiveness in the effect of SPF and conventional bird to the transmission rates (Supplementary material VI).

Based on the estimates for the infectious period, we conclude that *E. coli* carrying resistance genes can colonize broiler chickens for a lifelong period. However, the observations of the infectious period with an observed return to uncolonized state in our dataset were limited (7%) due to censoring of 187 out of 204 excreting periods. In spite of the limited data, our parameteric survival model utilized both the observed data and prior information from literature to estimate the probable infectious period (Ragione et al., 2005; Fong and Lehmann, 2022; Kalbfleisch, 1978). While the estimated infectious period of 56,678 hours (6 years) for *E. coli* carrying resistance genes is biologically implausible for broiler chickens, this estimate could be interpreted as lifelong colonization that broiler chickens typically experience, which lasts for only 40–56 days until they are slaughtered. This conclusion is consistent with Ragione et al. (2005), which showed an extended colonization period of 35–156 days for nalidixic-resistant pathogenic *E. coli* in layer chickens. Moreover, studies by Conway, Cohen (2015) and Stromberg et al. (2018) have demonstrated the superior adaptability of commensal *E. coli* to colonize animal guts compared to pathogenic *E. coli*, which supports our estimated longer infectious period. Despite the wide range of uncertainty in our analysis, inclusion of weakly informative priors in our model still has benefits. By incorporating prior knowledge from literature, the model was able to make more informed estimates even in the presence of limited data and high censoring rates. The prior provides a regularization effect that helps to stabilize the estimates and prevent overfitting, which can lead to erroneous conclusions. Overall, the use of weakly informative priors can improve the accuracy and reliability of model estimates, even in situations where data are limited and uncertainty is high.

Our study estimated the infectious period of piglets to be between 25 and 195 days, which we believe is reflective of real-life situations. The HPDI credible interval surrounding this estimate was narrower compared to that of broilers due to the greater number of observed return to uncolonized state. Although only 19% of the observed infectious periods had an observed return to uncolonized state (18 out of 93), the fact that there were any observed return to uncolonized states at all suggests that return to uncolonized state may occur after the end of the transmission experiment, and this knowledge provided more weight to our estimate of the infectious period. Furthermore, our estimate of the infectious period in piglets was consistent with previous colonization studies of *E. coli* in pigs, which reported colonization periods ranging from 1 to 5 months (Belloc et al., 2005; Johnson et al., 2015; Randall et al., 2018). However, animals in Belloc et al. (2005), Johnson et al. (2015), and Randall et al. (2018) were excreting beyond the end of the experiment; meaning that the reported colonization period was the same length as the experiment itself. In contrast, our estimate narrowed down the infectious period in piglets to a more specific timeframe of up to 7 months. This duration which institutes an entire growth cycle in certain pig population, such as finisher pigs. Overall, our results suggest that our approach was able to produce a realistic estimate of the infectious period of piglets that can be useful for future research and control strategies.

The estimation of the R_0 is important in understanding the dynamics of infectious diseases. In our study, we estimated the R_0 for different resistance genes, antibiotic treatments, and animal species. To calculate R_0, we combined the estimates of the infectious period and transmission rate from our hierarchical models. We assumed that these parameters are completely independent, which might cause our estimates to be overdispersed. While the wide intervals for R_0 migth represent overdispersion, we still believe our estimates provide valuable insights into the dynamics of *E. coli* carrying resistance genes in broilers and piglets.

Our Bayesian meta-analysis effectively identified factors related to the transmission rate of *E. coli* carrying resistance gene with greater precision, despite the limited number of studies and small sample sizes. To mitigate uncertainties stemming from small datasets, we harnessed raw longitudinal data from each study (Individual Participant Data) and implemented a Bayesian probabilistic framework that is capable of incorporating both prior knowledge and data. Instead of relying on summarized statistics across various studies, we employed a subgroup (pen-level) within the hierarchical model to curtail between-study heterogeneity. This tactic enabled us to focus on a common analytical unit resulting in more informed and accurate estimates of the factors driving the transmission (Riley et al., 2010).

It is important to note that with a limited number of studies, traditional frequentist assume large sample sizes (asymptotic), and can result in underestimation of between-study variance and overconfident confidence intervals (Mcneish, 2016). In contrast, Markov chain Monte Carlo (MCMC) in Bayesian approach explores the entire posterior distribution of the parameter and does not rely on asymptotic standard errors (Williams et al., 2018). As a result, Bayesian methods can provide more accurate estimates of between-study variance and are often recommended when dealing with meta-analyses of limited studies (Veroniki et al., 2014). Using this approach, we identified key factors contributing to the transmission dynamic of *E. coli* carrying resistance genes, including antibiotic treatment, resistance strain, and host species. The importance of each factor in determining the transmission dynamics of *E. coli* carrying resistance genes can vary depending on the specific resistance strain, animal species, and antibiotic treatment. For example, *E. coli* carrying resistance genes transfer faster in broiler chickens than in piglets, but only under no antibiotic treatment. Overall, our study highlights the complexity of the transmission dynamics of antibiotic resistant *E. coli* and emphasizes the need for comprehensive approach to mitigate the spread of antibiotic resistance. This multifaceted strategy could encompass interventions such as leveraging the animal's microbiome through probiotics to reduce transmission, implementing antibiotic stewardship to curtail antibiotic use, and exploring other variables that warrant further assessment. These combined efforts would work effectively toward controlling the propagation of antibiotic resistance.

The parameters identified in our study, such as the transmission rates and infectious periods of resistant *E. coli*, could be incorporated into more extensive simulation models. These models could aid in evaluating potential interventions to mitigate the spread of antibiotic resistance in livestock populations. Our study highlights the importance of rigorous analytical methods for small and limited data sets, which are necessary for accurately estimating these parameters and informing simulations.

The variation of transmission rate between resistance gene inoculation, antibiotic treatment, and animal species, highlighting the need for inclusion for additional transmission data. The uncertainty around infectious period estimates is also driven by unobserved return to uncolonized state due to short experimentation time. However, the Bayesian framework is flexible and can incorporate a wide range of data types and structure including data from field experiments and observational studies, enabling estimation of differences between experimental and field settings. To illustrate, our Bayesian-meta analysis model can incorporate field data through the use of priors. By incorporating field data into the priors, we can adjust our estimates to better reflect the actual values in the field. Additionally, our hierarchical modeling approach can account for differences between experimental and field settings by including additional levels in the model, such as

location or time, to capture the variability in the data. This allows for a more comprehensive and accurate representation of the transmission dynamics in real-world scenarios.

7. Conclusion

We believe our results are useful for simulation modelling of transmission dynamics of resistant bacteria in piglets (7–8 weeks old) and broilers (less than one week old), especially because in the Bayesian framework we have obtained a posterior distribution that can be used to include the uncertainty of the parameter estimates in such simulation models.

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CRediT authorship contribution statement

Clazien J. De Vos: Methodology, Supervision, Writing – review & editing. **Jaap J. A. Wagenaar:** Supervision, Writing – review & editing. **Arjan J. Stegeman:** Conceptualization, Project administration, Supervision, Writing – review & editing, Funding acquisition. **Egil A. J. Fischer:** Conceptualization, Formal analysis, Software, Supervision, Writing – review & editing. **Natcha Dankittipong:** Data curation, Methodology, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Jan Van Den Broek:** Methodology.

Declaration of Competing Interest

None

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.prevetmed.2024.106156.

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