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Transmission models of ESBL-producing *Escherichia coli* in Dutch broiler production chain

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Abstract

Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* in animals are considered a human health threat, because this type of bacteria can serve as a reservoir of antibiotic resistant genes and act as a continuous threat of the emergence of new resistant bacteria. Although the prevalence in broilers was drastically reduced, chicken meat still has the highest prevalence among meat products. Therefore, further control of the ESBL-producing *E. coli* in the broiler production chain is important to reduce public health risks. The main objectives of this study were to evaluate the effectiveness of intervention scenarios to control the transmission of ESBL-producing *E. coli* in the broiler production chain and to quantitatively estimate the risk to public health. In this study, we developed two different types of transmission models that described the observed time-related decline in prevalence during a production round: one with time-dependent decline in susceptibility and one with partial immunity to phylogenetic groups. Both models incorporated the environmental contamination effect between production rounds and within flocks. The parameter values, including transmission rate and recovery rate, were estimated by using Approximate Bayesian computation (ABC) method. We applied the models to broiler production chain and further added the effect of mixing eggs and chicks from different origins and adjusted the size of a flock and the number of farms to the Dutch situation. Both models were able to describe the observed dynamics within and between the production stages equally well and estimate the outcome of interventions quantitatively. Both indicated that improving farm management to eliminate the bacteria from the environment was the most effective intervention, which made the influence of the intervention on the outcomes robust. According to our models, chicken meat consumption was not a major risk factor for human carriage of the bacteria.

Keywords: Broiler production chain; ESBL; model

Plain language summary

Introduction: Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* in animals, especially in chickens, are considered a risk to human health, because this type of bacteria can be a continuous threat of the emergence of new bacteria that are resistant to antimicrobials. Antimicrobials are a kind of medicine that is widely used to treat human diseases such as penicillins, which are used to treat throat infections, meningitis, and syphilis. Disease caused by resistant bacteria cannot be cured with antimicrobials. Although the proportion of chickens with ESBL-producing *E. coli* drastically declined over the years in Dutch farms, chicken meat was still the most contaminated meat product among others. In addition, the bacteria can be found in all stages of the chicken production chain. The chain consists of mainly three different farm types: parent stock farms where chickens produce eggs, hatcheries where eggs are incubated, and broiler farms where chickens are fattened up for meat. Therefore, further control of ESBL-producing *E. coli* in the chicken production chain is important to reduce public health risks.
Objective: The main objectives of this study were to evaluate the effectiveness of intervention scenarios to control the transmission of ESBL-producing *E. coli* in the chicken production chain and to estimate the risk to public health.
Methods: In this study, we developed two different types of transmission models to describe the observed transmission dynamics within a chicken farm: one based on the immune development of chickens and one based on the infection characteristics of the bacteria. Both included the environmental contamination effect between production rounds and within flocks. The parameter values, which determine the spread of bacteria, were estimated by using the Approximate Bayesian computation (ABC) method. This method is a way to find the most appropriate parameter value by comparing the observed data with the simulated data. Then, we applied the models to the three stages in the chicken production chain and further added the effect of mixing eggs and chicks from different farms. The size of a flock and the number of farms were adjusted to the Dutch situation. Several intervention scenarios, including bird vaccination and farm disinfection, were applied to the models. Finally, using the simulated data, risk to human health was estimated.
Results: Two models were developed based on two different assumptions, which were development of immunity of the chickens and difference between the infection characteristics of the bacteria. Both models were able to capture the observed transmission dynamics. The proportion of infected chickens on the day of slaughter was 10.59% and 13.56%, respectively. The proportion of the Dutch population becoming infected by consuming chicken meat was estimated at 0.14% and 0.18%, respectively. If the bacteria in the farm environment were eliminated by cleaning and disinfection, the infected proportion of chickens would be reduced to 0.61% and 0.52%, respectively, and that of humans to 0.01%.
Conclusions: Both models were able to describe the observed transmission dynamics within and between the production stages equally well and estimate the outcome of the interventions quantitatively. Both indicated that improving farm management to eliminate the bacteria from the farm environment was the most effective intervention. According to our models, chicken meat was not a major source for transmitting the bacteria to humans.

Table of Contents

1. Introduction

Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* in animals are considered a human health threat, because this type of bacteria can serve as a reservoir of antibiotic resistant genes. ESBL-producing bacteria produce enzymes that inactivate beta-lactams, first- to third-generation cephalosporins, and aztreonam, which are widely used antimicrobials to treat infections in both human and veterinary medicine (Mevius et al. 2018; Chong, Ito, and Kamimura 2011). Although human carriage of such bacteria was mainly attributed to human sources (Mughini-Gras et al. 2019), and previous antimicrobial treatment and international travel were identified as the main risk factors for humans (Chong, Ito, and Kamimura 2011; Pitout 2009), the bacteria in animals are still a risk to public health. ESBL-producing bacteria can act not only as an infectious agent but also serve as a continuous threat of the emergence of new resistant bacteria (European Food Safety Authority and European Centre for Disease Prevention and Control 2022). The genes coding for ESBL-production can be transferred to other bacteria species by conjugation, which can eventually cause beta-lactam resistance in many bacteria species (Mevius et al. 2018).

In Europe, monitoring of the ESBL-producing bacteria in livestock has been carried out every year to track the possible source of emerging resistant bacteria. In the Netherlands, broilers, among other livestock species, had the highest prevalence of ESBL-producing *E. coli* in 2014 at around 66% ("Nethmap-MARAN 2021" 2021). However, by setting reduction targets on antimicrobial use in animals and restricting the use of ceftiofur in hatcheries (Mevius and Heederik 2014; "Nethmap-MARAN 2019" 2019), the prevalence of animals at slaughter was drastically reduced to 9.8% in 2020. On the other hand, at the consumption level, chicken meat still has the highest prevalence (9%) among meat products. Therefore, further control of the ESBL-producing *E. coli* in the broiler production chain is important to reduce public health risks.

The Dutch broiler production consists of several production stages, and ESBL-producing *E. coli* are detected at every level of the production chain (Dame-Korevaar 2020; Dierikx et al. 2013). The production chain starts with the import of Grandparents Stock (GPS) chicks. Their offspring become the Parent Stock (PS) and are raised to lay eggs on parent breeder farms. Then, PS-produced eggs are transported and incubated in hatcheries. Finally, the hatched chicks are transported to the broiler farms where they are reared until slaughter. ESBL-producing *E. coli* was observed in as young as two-day-old chicks on GPS farms and in one-day-old chicks on PS farms (Dierikx et al. 2013). In hatcheries, hatchlings are thought to become infected from contaminated eggshells, known as pseudo-vertical transmission (Projahn et al. 2017; Oikarainen et al. 2019; Mezhoud et al. 2016) and the prevalence in hatcheries ranged from 0% (Oikarainen et al. 2019) to 3.8% (Mezhoud et al. 2016). In broiler farms, bacteria can be transmitted directly from infected chicks from the hatcheries and also indirectly via the remaining environmental contamination from the previous production round (Dierikx et al. 2013). ESBL-producing *E. coli* can be found in as young as one-day-old broiler chicks (Laube et al. 2013; Dierikx et al. 2013; Huijbers et al. 2016). In the longitudinal study by Huijbers et al. (2016), the prevalence in broilers on the day of arrival at the farm was about 30% and then increased to as high as 100% on day 3. Then it decreased to 20% on day 42 and went up to 40% on day 70. A similar trend was also reported in an experimental study in PS birds (Dame-Korevaar et al. 2017); the prevalence began at around 90% on day 7 and started to decrease in week 11 from 46% to finally 1% in week 19. Most ESBL-producing *E. coli* isolates are obtained from healthy animals and generally have little implication for hosts' health (Kuhnke 2020).

Improvements in biosecurity and hygiene management, disinfection of eggs, and vaccination have been implemented in poultry farms to reduce the prevalence of the bacteria (Becker et al. 2021; Hao et al. 2013; Sadeghi et al. 2018; Swelum et al. 2021; K. Y. Luyckx et al. 2015; Mo et al. 2016; Motola, Hafez, and Brüggemann-Schwarze 2020). Competitive exclusion (CE) is a method to protect chicks from undesirable bacteria, including *Salmonella*, by feeding non-pathogenic intestinal bacteria. The effects of CE on ESBL-producing *E. coli* were studied in experimental settings and considered to be useful to reduce transmission and prevent colonization, especially when applied to young chicks for several days (Ulrich Methner and Rösler 2020; U. Methner, Friese, and Rösler 2019; Dame-Korevaar, Fischer, et al. 2020; Dame-Korevaar, Kers, et al. 2020; Nuotio, Schneitz, and Nilsson 2013; Ceccarelli et al. 2017).

Since large-scale intervention studies in the broiler production chain cannot be carried out due to cost and practical issues, several mathematical models were developed to simulate the transmission and assess the effectiveness of interventions (Plaza Rodríguez, Correia Carreira, and Käsbohrer 2018; Huijbers et al. 2016; Dekker 2019). Plaza et al. (2018) incorporated several production stages and transportation effects into their transmission model and showed a difference between animal and flock transmission dynamics (Plaza Rodríguez, Correia Carreira, and Käsbohrer 2018). However, they did not consider the effect of mixing birds and eggs from different origins, or the flock size and numbers. In their study, transmission parameters were set at a constant value, although several studies have reported fluctuation of the ESBL-producing *E. coli* prevalence as birds age (Huijbers et al. 2016; Dierikx et al. 2013; Dame-Korevaar et al. 2017; Laube et al. 2013; Apostolakos et al. 2019). These age-related declines in the prevalence are possibly due to a change in susceptibility caused by shifts in the microbiota (Diarra et al. 2007) or changes in phylogenetic groups (Apostolakos et al. 2019).

Therefore, we included the effect of mixing eggs and chicks from different origins and adjusted the size of a flock and the number of farms to the Dutch situation. Most importantly, we developed two different types of within-flock transmission models, one with the age-related decline in susceptibility and another with partial immunity to phylogenetic groups. We further incorporated the environmental contamination effect between production rounds and within flocks. The parameter values, including transmission rate and recovery rate, were estimated by using Approximate Bayesian computation (ABC) method. An advantage of the ABC method is that it approximates the posterior distributions of the parameters from a generative model by comparing the simulated data with the observed data without specifying a likelihood function. The main objectives of this study are to evaluate the effectiveness of the intervention scenarios to control the transmission of ESBL-producing *E. coli* in the broiler production chain and to estimate the risk to public health.

2. Methods

2.1. Overview of the transmission dynamics

In this study, the following three production stages were considered: PS breeder farms (n=195), broiler hatchery farms (n=13), and broiler production farms (n=637). The number of farms approximated the Dutch situation ("CBS Statline" 2022a; Ellen et al. 2012). Transmission between production stages occurred by transporting infected animals, and transmission within the PS and broiler farms occurred directly from infectious birds and/or indirectly through the contaminated environment (Figure 1). In the PS farms, 2,000 birds were continuously renewed every 66 days, while the broiler farms followed an all-in-all-out system with a vacancy period of 7 days. In the broiler farms, the transmission also included the effect of the contaminated environment from the previous production round. As for the hatcheries, a certain proportion of eggs from the infected parent stocks hatched as infected chicks. Horizontal transmission did not occur in the hatcheries.

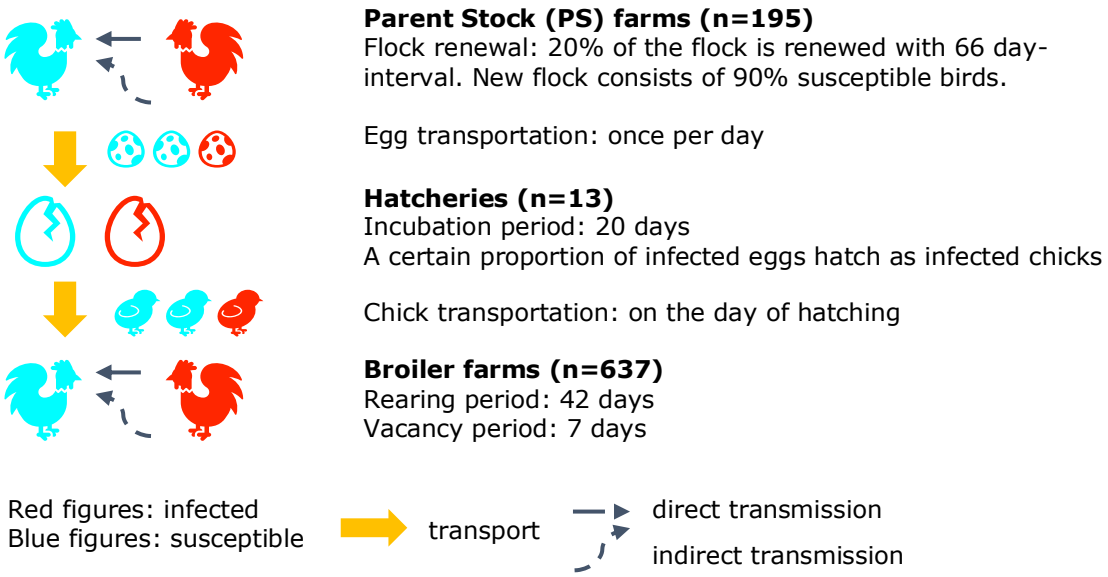


***Figure 1**. Between and within transmission routes of ESBL-producing E. coli in the three production stages of the broiler production pyramid model.*

2.2. Transmission model

2.2.1. Transmission and movement between the production stages

To study the transmission in a broiler production chain, multiple production stages were connected in one model. This was done by utilizing the ability in the R package SimInf (Widgren et al. 2019) that schedules the demographic and movement events to modify the state of a production stage at a pre-defined time. In the model, four types of poultry movements were defined: enter, internal transfer, external transfer, and exit. The enter events added new PS birds to a production stage. The internal transfer events moved PS birds from one age category to another within one production stage. External transfer events moved eggs and chicks from one production stage to another. Finally, exit events removed PS birds and broilers from the stage to slaughter.

In this study, around 2,000 18-week-old PS birds were brought to a PS breeder farm every 66 days with a prevalence of 10% by an enter event (the numbers were randomly generated and rounded, thus were not exactly 2,000). Then, by an internal transfer event, the PS chicks changed the age category five times with a 66-day interval. After finishing the fifth category, when the chick was around 65 weeks old, it was removed by an exit event. In short, a PS farm consisted of five different age categories with 2,000 birds per category. A PS bird had contact with all other PS birds on the farm. Eggs were laid at a rate of 0.065 per day (b) and transported daily to hatcheries through an external transfer event. All eggs from susceptible PS birds were assumed to be uncontaminated. As for the eggs from infected PS birds, it was assumed that pseudo-vertical transmission (l) occurred at a rate of 0.009 and of those contaminated eggs infected chicks hatched at a rate of 0.01 (hatching colonization rate (m)). After 20 days of incubation (hatching rate (δ)), the hatched chicks were transported to broiler farms by an external transfer event. After 42 days of the rearing period, the broilers were slaughtered through an exit event. The broiler farms used an all-in-all-out system with a 7-day interval, meaning that all birds on a farm were of the same age. The time of the movements and the destination farms were fixed deterministically, but the numbers of moved birds and eggs were chosen stochastically. All values related to population dynamics and transmission between the production stages are summarized in Tables 1 and 2.

Table 1. *Parameters and values for population dynamics in the SIS and SISIR models.*

Notation	Value	References
Duration in Parent Stock farms	47 weeks	-
Proportion of renewal of Parent Stock birds	20%	-
Proportion of susceptible birds in renewed Parent Stock birds	90%	-
Interval of population renewal in Parent Stock farms	66 days	-
Duration in hatcheries (incubation period)	20 days	-
Duration in broiler farms	42 days	-
Interval between broiler production rounds	7 days	-
Laying rate (b)	0.065	-
Hatching rate (δ)	0.05	-
Daily death rate (i)	0	-
Pseudo vertical transmission rate (l)	0.009	0.018 (0, 0.036) Projahn *et al*., 2017
Hatching colonization rate (m)	0.01	0.011 (0, 0.022) Projahn *et al*., 2017

2.2.2. Transmission within a flock (PS farms and broiler farms)

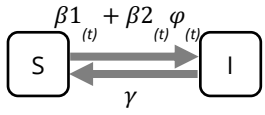
We used two different stochastic compartment models as the basis of within-flock transmission: the susceptible-infected-susceptible (SIS) model and the susceptible-infected-susceptible-infected-recovered (SISIR) model (Figure 2). We decided to use these two models as other models were unlikely to describe the transmission dynamics. For example, the SI model, in which infected birds stay infected for the rest of its life, or the SIR model, in which a recovered bird from a single infection acquires immunity, was not suitable, given the fluctuation in the prevalence observed in several studies (Laube et al. 2013; Huijbers et al. 2016; Dierikx et al. 2013; Dame-Korevaar et al. 2017). We did not include a latent period in the model because the excretion of the bacteria begins within 24 hours after inoculation (Ceccarelli et al. 2017).

In the SIS model, a susceptible bird (S) acquired bacteria directly from an infected bird (I) and indirectly from the environment at a rate $\beta 1$ and $\beta 2$, respectively. The indirect transmission also included the infection pressure from the environment (φ), which was calculated from the shedding rate of bacteria from the infected birds (θ) and the survival rate of the bacteria in the environment (ρ). The transmission rates were reduced over time (ψ) to mimic age-related immunity development. An infected bird recovered at a rate γ and became susceptible again (Tables 2 and 3).

As for the SISIR model, the model distinguished infections per phylogenetic group. A susceptible bird (S_i) became infected indirectly via the environment with one of the three phylogenetic groups (i) at a rate $\beta 2_i$ with environmental infection pressure φ calculated as mentioned above. Then the infected bird (I_i) recovered at a rate γ_i and became susceptible again to another phylogenetic group. After two infections with different phylogenetic types, a bird recovered (R) and became immune to infection. Transmission and recovery rates were assumed to be specific to each phylogenetic group (Tables 2 and 3). In this model, the transmission rate was assumed to be time-independent and stable for the entire period.

We also explored the possibility of transmission happening either directly or indirectly for the SIS model. As for the SISIR model, another model that incorporated only two phylogenetic groups was developed (Supplementally 1 and 2). All models were able to fit the observed data but based on the biological plausibility, these were not used in the further discussion. Here, direct transmission occurred via contact between infected and susceptible animals and indirect transmission occurred via the pathogens in the environment excreted from infectious animals (Cortez and Weitz 2013). Although the main transmission route is still unknown (Dame-Korevaar, Fischer, van der Goot, Stegeman, et al. 2019), we expected that indirect transmission from the faeces and the environment is the main source of infection.

(1) SIS model



S: susceptible
I: infected
R: recovered
β1: direct transmission rate
β2: indirect transmission rate
φ: environmental contamination
γ: recovery rate
(t): time-dependent transmission reduction (ψ)
1~3, i: phylogenetic type

(2) SISIR model

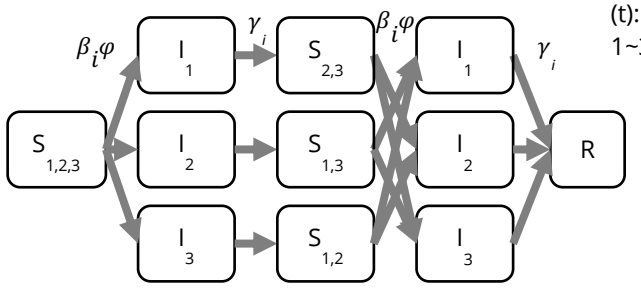


Figure 2. *Compartment models. (1) SIS model with time-dependent transmission reduction. Transmission can occur directly and indirectly. (2) SISIR model with three phylogenetic groups. A susceptible bird (S_i) becomes infected with one of the three phylogenetic types and becomes an infected bird (I_i). After recovery from the first infection, the bird becomes susceptible again and can acquire another phylogenetic type. After two infections, the bird becomes immune to the bacteria (R). Transmission occurs indirectly without time-dependent transmission reduction.*

Table 2. *Description of parameters for transmission within a flock and between production stages.*

Parameter	Description
β1(t)	Time-dependent direct transmission rate for the SIS model
β2(t)	Time-dependent indirect transmission rate for the SIS model
$\beta 2_i$	Indirect transmission rate for phylogenetic type *i* for the SISIR model
φ	environmental contamination
ψ	transmission reduction for the SIS model
γ	Recovery rate for the SIS model
γ_i	Recovery rate from phylogenetic type *i* for the SISIR model
θ	Bacterial shedding rate
ρ	Bacteria survival rate in the environment
b	Laying rate
δ	Hatching rate
i	Daily death rate
l	Pseudo vertical transmission (egg contamination rate)
m	Hatching colonization rate

Table 3. *Transition equations on infectious states.*

Transition	Description	Model	Equation for rate of change
S→I	Transition from susceptible (*S*) to infectious (*I*)	SIS	$-\left(\beta 1(t)\frac{I}{N}+\varphi(t)\beta 2(t)\right)S$
	Transition from susceptible to infectious with phylogenetic group *i*	SISIR	$-\varphi\beta 2_i S$
I → S	Transition from infectious to susceptible	SIS	$-\gamma I$
	Transition from infectious with phylogenetic group *i* to susceptible	SISIR	$-\gamma_i I_i$
I → R	Recovery (*R*) from infectious with phylogenetic group *i*	SISIR	$-\gamma_i I_i$
EE → S	Hatching of susceptible chicks from uncontaminated eggs (*EE*)	SIS and SISIR	δEE
EI→S	Hatching of susceptible chicks from contaminated eggs (*EI*)	SIS and SISIR	$\delta(1-m)EI$
EI → I	Hatching of infectious chicks from contaminated eggs	SIS and SISIR	δmEI

N: Total number of animals. β1: Direct transmission rate in the SIS model. $\beta 2_i$: Indirect transmission. *i* denotes phylogenetic type *i* in the SISIR model. φ: environmental contamination pressure. γ_i: Recovery rate. *i* denotes phylogenetic type *i* in the SISIR model. δ: Hatching rate, m: Hatching colonization rate.

2.3. Parameterization of within-flock transmission dynamics

Within-flock transmission was parameterized using a longitudinal study on a Dutch organic broiler farm by Huibers et al. (2016). The study was conducted between June and November 2013. Briefly, cloacal swabs were obtained from 100 broilers (80 tagged and 20 untagged) on days 1, 3, 4, 7, 10, 42, and 70 and analysed for the presence of ESBL-producing *E. coli*. The positive samples were further examined for phylogenetic group determination. The prevalence in tagged broilers was used in the SIS model, and the prevalence in total broilers (tagged and untagged) was used for the SISIR model.

The parameters used in the within-flock models were fitted using the Approximate Bayesian Computation Sequential Monte Carlo (ABC-SMC) algorithm (Toni et al. 2009) implemented in the SimInf package (Widgren et al. 2019). Briefly, the ABC method consists of three steps. First, the parameters are sampled from prior distributions. Then, the generative model simulates a dataset using the parameters. Third, posterior distributions of the parameters are obtained by comparing the simulated data with the observed data and accepting proposed parameter values when the difference is within a pre-defined threshold. In our study, first, the models were run 100 times using random values from the prior parameter distributions, which were assumed to be uniform between 0 and 10 for transmission rate (β) or 0 and 1 for other parameters (ψ, γ, θ, ρ). The prevalence was then calculated for each time point. Finally, the distance between the generated prevalence and the observed prevalence was obtained by the sum of squared differences of the prevalence. The number of particles, the tolerance, the proportion of tolerance, and the generations was set to 500, 10,000, 0.9 and 100, respectively. The median values of the posterior distributions from 10 iterations were used to obtain the results for the basic scenario.

2.4. Initialization

Simulations were started by introducing around 2,000 PS birds per age category with a 10% prevalence. For the SISIR model, the prevalence of each phylogenetic group was assumed to be 92.3%, 7.7%, and 0.4%, respectively. The initial environmental infectious pressure was assumed to be zero. The models were simulated for 4000 days with a burn-in period of 3000 days to eliminate the influence of these starting values.

2.5. Evaluation of control measures

Currently, CE, vaccination, and hygiene improvement are the three major interventions that are considered to reduce the prevalence of ESBL-producing *E. coli*. in practice. The effectiveness of these control measures was evaluated by changing the values of the corresponding parameters. CE

and vaccination were translated as a reduction in the shedding rate and the transmission rate, respectively. Improvement in hygiene was reflected by decreasing in the survival rate of bacteria in the environment. In short, four types of intervention scenarios were tested: (1) Reduction of shedding rate in PS birds and broilers, (2) Reduction of transmission rate in PS birds and broilers, (3) Decreasing the bacteria survival rate during the vacancy period in broiler farms, and (4) Decreasing the survival rate of the bacteria in PS and broiler farms. All reduction rates were determined based on literature as summarized in Table 4. Previous studies on CE reported a reduction of two to five log CFU/g bacteria in faeces and caecal content, thus the shedding rate was reduced to 1.0×10^{-2}, 1.0×10^{-3}, and 1.0×10^{-5} of the original value (Nuotio, Schneitz, and Nilsson 2013; Ceccarelli et al. 2017; U. Methner, Friese, and Rösler 2019; Ulrich Methner and Rösler 2020). CE also reduced the transmission rate to 1.5 to three-fold (Dame-Korevaar, Fischer, et al. 2020), therefore, as a second intervention scenario, the transmission rate was reduced to 0.7 and 0.3 of the original value. Some studies reported that cleaning and disinfection almost eliminated the bacteria in the environment, thus the bacteria survival rate in the environment was reduced to 0.5, 0.25, 1.0×10^{-2}, and 0 of the original value (K. Y. Luyckx et al. 2015; K. Luyckx et al. 2015; Gradel et al. 2004). In addition, a 1.0×10^{-3} reduction in the transmission rate was also tested to compare with a 1.0×10^{-3} reduction in the shedding rate. Each scenario was run 10 times in both models and the mean prevalence at slaughter in broiler farms was compared to that of the basic scenario.

Table 4. *Intervention scenarios and adjusted parameter values.*

Parameters	Reduction*	Related Interventions (references)
Shedding rate (Parent Stock and broilers)	1.0×10^{-2}	CE treatment, vaccination (Nuotio *et al.*, 2013, Ceccarelli *et al.*, 2017, Methner *et al.*, 2019, Methner *et al.*, 2020)
	1.0×10^{-3}	
	1.0×10^{-5}	
Transmission rate (Parent Stock and broilers)	0.7	CE treatment, vaccination, improvement of hygiene (indirect transmission) (Dame-Korevaar *et al.*, 2020)
	0.3	
	1.0×10^{-3}	
Bacteria survival rate during the vacancy period (Broilers)	0.5	Cleaning and disinfection (Luyckx *et al.*, 2015, Luyckx *et al.*, 2015, Gradel *et al.*, 2004, Hao *et al.*, 2013)
	0.25	
	1.0×10^{-2}	
	0	
Bacteria survival rate (Parent Stock and broilers)	1.0×10^{-2}	Cleaning and disinfection
	0	

*Reduction shows the reduction from the original value (e.g., reduction of 1.0×10^{-2} means the value used was the 1.0×10^{-2} of the original parameter value).

2.6. Sensitivity analysis

Sensitivity analysis was performed to assess the impact of variation in parameters on the outcome. All parameters in the models were examined except for those determined the demography. Using Latin Hypercube Sampling (LHS), ABC-fitted parameters were sampled from the 2.5% and 97.5% percentiles of the posterior distribution (Table 5). For pseudo vertical transmission and hatching colonization rates, the 2.5% and 97.5% percentiles from the literature were used (Projahn et al. 2017) (Table 1). The sample size was set to 10 times the number of parameters used in the corresponding model. The regression coefficients were obtained between the sampled parameters and the following three outputs on simulation day 4000: (1) the average animal level prevalence for each production stage (the sum of the animal level prevalence in all flocks divided by the number of flocks), (2) the flock level prevalence for each production stage (the proportion of infected flocks), and (3) the mean animal level prevalence at slaughter (the sum of the animal level prevalence divided by the number of broiler farms on day 42 in a production cycle). Broiler farms that are in the vacancy period were excluded from the outcomes (1) and (2).

2.7. Quantitative Microbiological Risk Assessment

Simulated prevalence at slaughter in broiler farms (on day 4000 of the simulation period) was used to calculate human prevalence due to consumption of chicken meat. The following factors were considered in the calculation: (1) the reduction of prevalence from raw chicken meat to chicken at the moment of consumption (0.102) (Evers et al. 2017), (2) the probability of becoming an ESBL-producing *E. coli* carrier after consuming a chicken portion (1.19×10^{-3}) (E. Evers, personal communication, February 14, 2022)), (3) the number of chicken portion consumed per year by the population in the Netherlands (1.75×10^{9}) (Evers et al. 2017), (4) the mean duration of ESBL-producing *E. coli* carriership (1.1 years) (Teunis et al. 2018), and (5) the population of the Netherlands (1.741×10^{7}) ("CBS Statline" 2022b).

First, animal level prevalence per flock was multiplied by the reduction of prevalence from raw chicken meat to chicken at the moment of consumption (0.102) to obtain prevalence at consumption level (*A*). Then (*A*) was multiplied by the size of the flock and the probability of becoming an ESBL-producing *E. coli* carrier after consuming a portion of chicken (1.19×10^{-3}), then was summed over all flocks to obtain (*B*). The yearly incidence of ESBL-producing *E. coli* in humans in the Netherlands (*C*) was then calculated by multiplying (*B*) by the number of chicken portion consumed per year by the population in the Netherlands and divided by the total number of broilers. Finally, the prevalence of ESBL-producing *E. coli* in humans was obtained by (*C*) multiplied by the mean duration of ESBL-producing *E. coli* carriership divided by the population of the Netherlands (Figure 3).

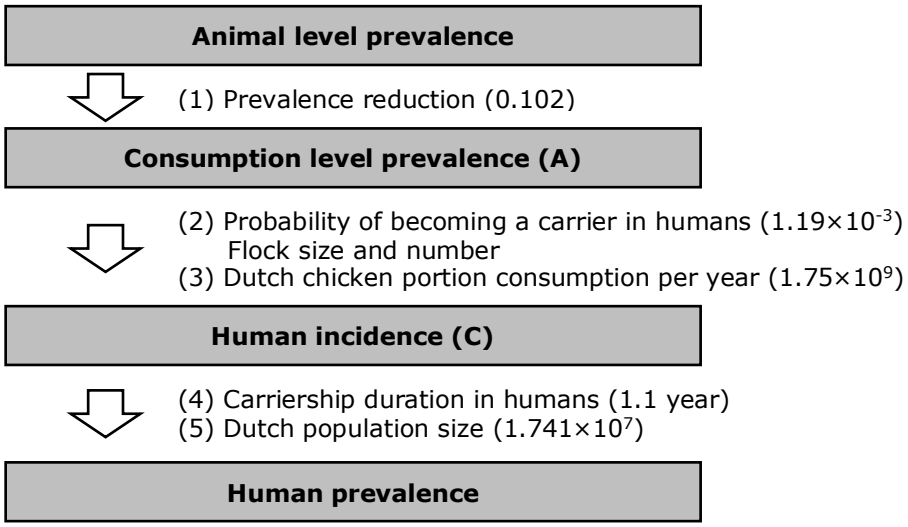


Figure 3. *Assessment of human prevalence due to consumption of chicken meat.*

2.8. Simulation method

The transmission and ABC simulations were performed using the SimInf package (version 8.2.0.9000) in R (version 4.0.4). SimInf is a modelling framework for data-driven modelling and simulation of stochastic disease spread within and among subpopulations (Widgren et al. 2019).

3. Results

3.1. Population and dynamics

At the end of the simulation (day 4000), for the SIS model, an average of 9,969 PS birds, 199,291 eggs, and 9,719 broilers were present per farm (broiler farms in the vacancy period are excluded). For the SISIR model, the numbers were 9,973, 199,492, and 9,724, respectively. Of the 637 broiler farms, 91 were in the vacancy period and 13 were on the day of slaughter. All results presented in this paper, unless otherwise stated, were analysed using data on simulation day 4000 from 10 iterations.

3.2. Parameterization of within-flock transmission dynamics

We fitted data from a longitudinal study in a Dutch organic broiler farm (Huijbers et al. 2016) to the within-flock models using the ABC method. The ABC-fitted posterior parameter distributions are given in Table 5. Both SIS and SISIR model were able to capture the fluctuation in prevalence that was observed in the study (Figure 4). In the SIS model, indirect transmission had a greater influence on the spread of the bacteria compared to direct transmission. In the SISIR model, the estimated transmission rates per phylogenetic group were more or less in the same range, but the infection duration varied among the groups.

Table 5. *Prior distributions and medians of the posterior distribution of the parameters.*

Parameter	Prior distribution	Posterior distribution (95% CI)	
		SIS model	SISIR model
$\beta 1$	Uniform (0, 10)	2.36 (0.20, 5.36)	-
$\beta 2$	Uniform (0, 10)	5.16 (0.30, 9.57)	-
$\beta 2_1$	Uniform (0, 10)	-	5.01 (0.57, 9.63)
$\beta 2_2$	Uniform (0, 10)	-	4.53 (0.65, 9.47)
$\beta 2_3$	Uniform (0, 10)	-	5.34 (0.94, 9.51)
ψ	Uniform (0, 1)	0.69 (0.34, 0.98)	-
γ	Uniform (0, 1)	0.09 (0.02, 0.19)	-
γ_1	Uniform (0, 1)	-	0.05 (0.03, 0.09)
γ_2	Uniform (0, 1)	-	0.35 (0.052, 0.90)
γ_3	Uniform (0, 1)	-	0.31 (0.02, 0.82)
Θ	Uniform (0, 1)	0.51 (0.04, 0.96)	0.52 (0.03, 0.97)
ρ	Uniform (0, 1)	0.49 (0.04, 0.96)	0.77 (0.11, 0.99)

$\beta 1$: Direct transmission rate for the SIS model. $\beta 2_i$: Indirect transmission rate. *i* denotes phylogenetic type *i* in the SISIR model. ψ: transmission reduction rate. γ_i: Recovery rate. *i* denotes phylogenetic type *i* for the SISIR model. θ: Bacterial shedding rate. ρ: Bacteria survival rate in the environment.

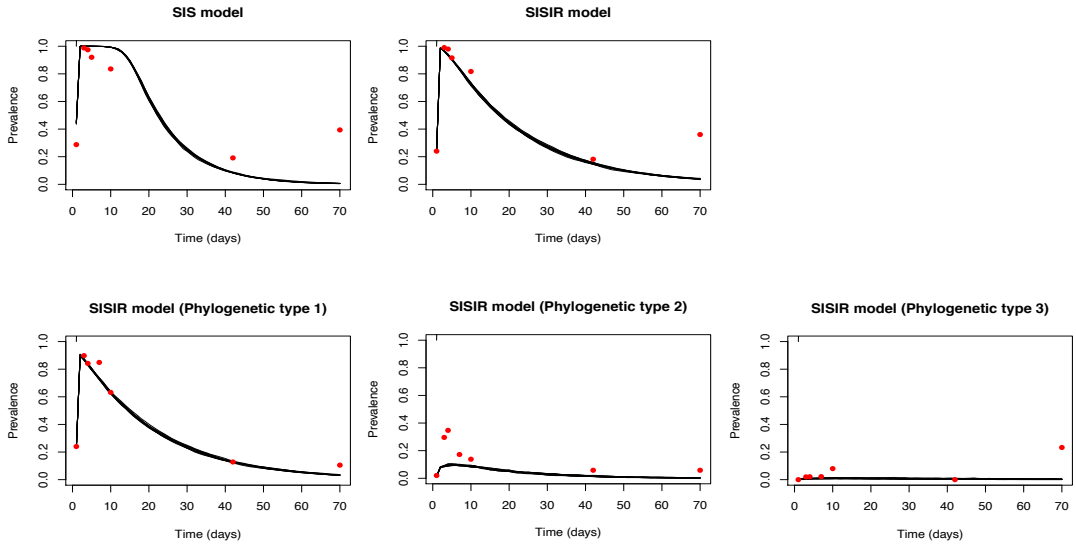


Figure 4. *ABC-simulated prevalence (black line) and observed data (red points). Top left: SIS model. Top right: SISIR model. Bottom: Specific phylogenetic groups in the SISIR model.*

3.3. Transmission between the production stages

The following outcomes of the SIS and SISIR model were used for analysis: the mean of the animal and flock level prevalence per production stage, the mean of the animal and flock level prevalence at slaughter, and human prevalence due to consumption of chicken meat. The animal

level prevalence was derived by averaging the weighted average per model run over iterations. The flock level prevalence (the proportion of infected flocks) was calculated by dividing the number of flocks with at least one infected animal by the number of all flocks per run and averaged over iterations. The prevalence in broilers at slaughter time was obtained on day 42 of the production round.

Each prevalence is presented as a percentage with 95% credible intervals (CI) and the standard deviation averaged over iterations in Table 6. The standard deviation (SD) shows the variation between flocks, and the 95% CI of the standard deviation shows the variation between the model iterations. For example, the mean animal prevalence in the broiler farms in the SIS model was 60.22% (59.56, 60.54 95%CI) with a standard deviation of 35.73% (35.57, 35.94 95%CI). This means the mean animal prevalence ranged from 59.56% to 60.54% (95%CI) between the simulations and it varied from ± 35.57% to 35.94% (95%CI) between flocks. The reason for the large standard deviation, unlike other production stages, is because the flocks followed different production cycles (e.g., one flock is on day 1, when almost all birds are susceptible while the other flock is on day 4 when almost all birds are infected). The flock prevalence was 99.23% (94.04, 100.00 95%CI) with a standard deviation of 2.43% over the iterations. The human prevalence by consuming meat from these broilers was calculated at 0.14% with almost no variation over the prevalence and the iterations.

Overall, the animal level prevalence started at around 7% in PS, decreased to one hundredth in hatcheries, and increased in broilers (Figure 5). The animal level prevalence in broilers was higher than that of the PS birds. This can be explained by the duration of the production cycle. Birds in the PS farms were older than the broilers which implied that the transmission rate was lower (SIS model) or the birds were already recovered from two infections (SISIR model).

Table 6. *The mean and standard deviation of simulated flock and animal level prevalence at all production stages and human prevalence due to consumption.*

Stage	SIS model	SISIR model
Parent Stock	7.34 (7.32, 7.35) ± 7.67 (7.66, 7.69)	6.82 (6.81, 6.84) ± 5.80 (5.78, 5.83)
	100.00 (100.00, 100.00) ± 0.00	100.00 (100.00, 100.00) ± 0.00
Hatcheries	0.07 (0.06, 0.07) ± 0.03 (0.03, 0.03)	0.06 (0.06, 0.07) ± 0.02 (0.02, 0.02)
	100.00 (100.00, 100.00) ± 0.00	100.00 (100.00, 100.00) ± 0.00
Broilers	60.22 (59.56, 60.54) ± 35.73 (35.57, 35.94)	43.19 (42.87, 43.65) ± 25.95 (25.70, 26.18)
	97.29(96.79, 97.76) ±0.34	96.83 (96.34, 97.78) ± 0.49
Slaughter	10.59 (10.10, 10.77)±0.59 (0.25, 2.44)	13.56 (11.88, 14.36) ±2.42 (1.20, 5.43)
	99.23 (94.04, 100.00) ± 2.43	96.15 (84.62, 100.00) ± 6.54
Human	0.14 (0.14, 0.14) ± 0.00	0.18 (0.16, 0.19) ± 0.01

Top row: Mean animal-level prevalence in % (95% CI) ± SD (95% CI). Bottom row: flock-level prevalence in % (95% CI) ± SD. The 95% CI of the mean prevalence shows the range over iterations. The SD shows the variation between flocks within the simulation. The 95% CI of the SD shows the variation between the iterations.

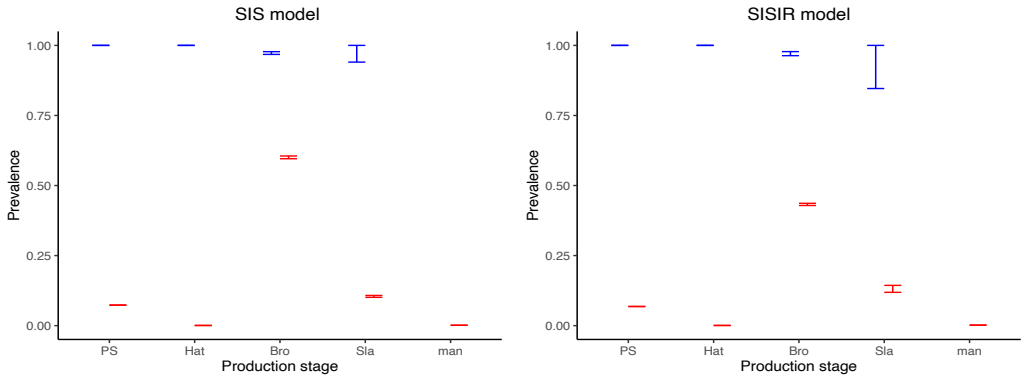


Figure 5. *The 95% CIs of the flock (blue) and animal (red) prevalence at all production stages and human prevalence from chicken consumption for the SIS model (left) and SISIR model (right).*

3.4. Intervention scenarios

Figure 6 shows the effect of the intervention scenarios on the animal level prevalence at slaughter and transmission to humans (Supplementally 3). In the SIS model, both broiler and human prevalence were reduced by the four types of interventions: (1) reduction of the shedding rate, (2) reduction of the transmission rate, (3) reduction of the bacteria survival rate during the vacancy period in broiler farms, and (4) reduction of the bacteria survival rate in PS and broiler farms. To reduce the prevalence, a reduction of more than 1.0×10^{-2} and 0.3 was needed for the shedding and transmission rate, respectively. The impact of the reduction of the shedding and the transmission rate on the outcome was compared by reducing both rates to the 1.0×10^{-3} of the original value. The reduction of the transmission rate had a larger negative impact on the prevalence compared to the reduction of the shedding rate. The reason for this is the former had influence on both direct and indirect transmission while the latter only affected indirect transmission.

As for the SISIR model, only interventions (3) and (4) were able to decrease the prevalence. In both settings, the prevalence decreased when the survival rate of the bacteria was reduced to more than 1.0×10^{-2} of the original value. However, the prevalence increased when the shedding rate was reduced to 1.0×10^{-5} of the original value. This was because the reduction of the shedding rate slowed the transmission between the birds, resulting in fewer recovered birds after two infections compared to the basic scenario; there were 89,540 and 2,166 more birds in the first infection and second infection, respectively, and 321,645 fewer recovered birds.

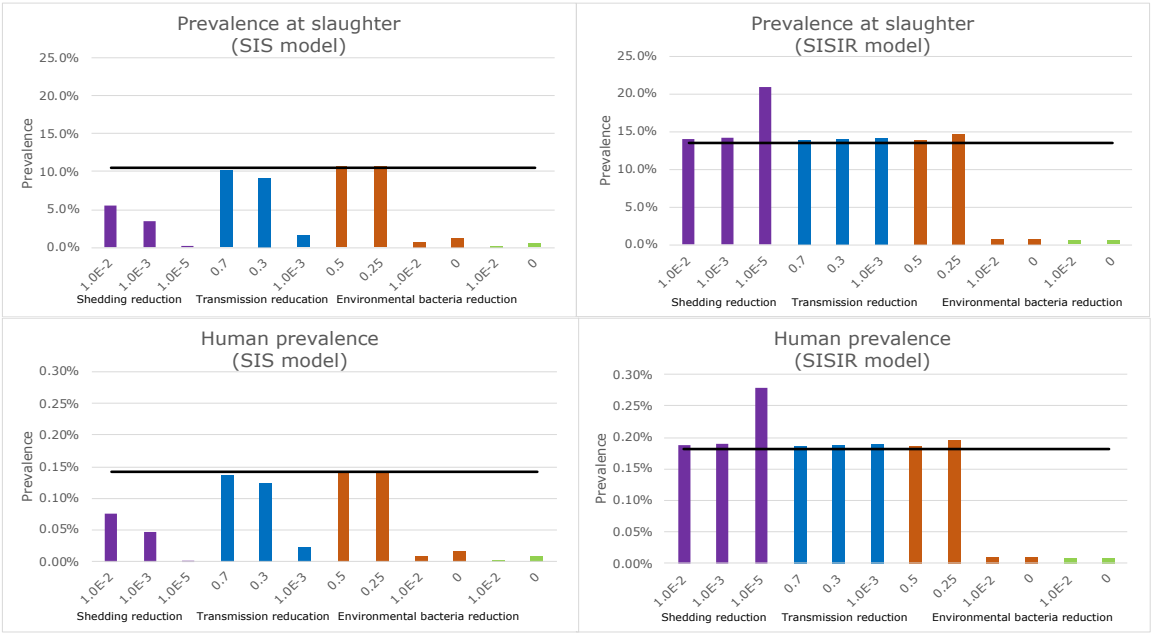


Figure 6*. Effect of interventions on the simulated animal-level prevalence at slaughter (Top) and human prevalence (Bottom) for the SIS model (left) and SISIR model (right). X axis: reduction of parameters. Horizontal black line: the prevalence from the base scenario. Purple bar: reduction in the shedding rate. Blue bar: reduction in the transmission rate. Orange bar: reduction in the bacteria survival rate during vacancy period. Green bar: reduction in the bacteria survival rate.*

3.5. Sensitivity analysis

Table 7 shows the results of the regression coefficient analysis for both models. For the SIS model, a strong negative correlation between animal level prevalence and recovery rate (γ) was observed in PS and broiler farms. The animal level prevalence in broilers was also strongly negatively correlated with the transmission reduction (ψ) and positively with the pseudo vertical transmission rate (l). Similarly, at the flock level, the prevalence was strongly negatively correlated with γ in PS farms. In broiler farms, the bacteria survival rate in the environment (ρ) and l had a positive effect on the flock prevalence. The animal level prevalence at slaughter was strongly negatively correlated with γ and ψ. For the SISIR model, the animal prevalence was strongly negatively

correlated with the recovery rate for phylogenetic group 1 (γ_1) in PS and broiler farms. The animal level prevalence in broiler farms was strongly positively correlated with *l* and the hatching colonization rate (*m*). The same trend was seen in flock level prevalence and animal prevalence at slaughter in broiler farms. Here a strong correlation is used when the coefficient was less than -0.5 or more than 0.5.

Table 7. Regression coefficients of the model parameters on the outcomes.

		β2	**B2₁**	**γ**	**γ₁**	**γ₂**	**γ₃**	**Θ**	**ρ**	**ψ**	**l**	**m**
SIS model												
(1)	PS	0.0	-	**-0.5**	-	-	-	-	-	-0.1	-	-
	Hat	0.0	-	0.0	-	-	-	-	0.0	0.0	0.1	-
	Bro	-	-	**-1.6**	-	-	-	-	0.4	**-0.7**	**4.4**	-
(2)	PS	-	-	**-0.5**	-	-	-	-	-	-0.1	-	-
	Hat	-	-	-	-	-	-	-	-		-	-
	Bro	-	-	-	-	-	-	-	**0.5**	-	**7.2**	-
(3)		-	-	**-2.4**	-	-	-	-	0.2	**-0.6**	-	-
SISIR model												
(1)	PS	-	0.0	-	**-1.0**	0.0	0.0	-	-	-	-	-
	Hat	-	-	-	0	-	0.0	-	-	-	0.1	-
	Bro	-	-	-	**-1.1**	-	-	-	-	-	**2.3**	**3.7**
(2)	PS	-	-	-	-	-	-	-	-	-	-	-
	Hat	-	-	-	-	-	-	-	-	-	-	-
	Bro	-	-	-	**-1.5**		0.0	0.0			**5.8**	**9. 6**
(3)		-	-	-	**-0.7**		0.0	-	-	-	**0.8**	**1.4**

(1) the animal prevalence per production stage, (2) the proportion of infected flocks per production stage, and (3) the prevalence at slaughter. Coefficients less than -0.5 or more than 0.5 are in bold. ($p < 0.05$)
PS: Parent Stock. Hat: Hatcheries. Bro: Broiler. $\beta2_i$: Indirect transmission rate. *i* denotes phylogenetic type *i* in the SISIR model. γ_i: Recovery rate. *i* denotes phylogenetic type *i* for the SISIR model. θ: Bacterial shedding rate. ρ: Bacteria survival rate in the environment. ψ: transmission reduction rate. l: Pseudo vertical transmission rate. m: Hatching colonization rate.

3.6. Quantitative Microbiological Risk Assessment

The simulated animal level prevalence at slaughter on broiler farms was used to evaluate the risk to humans from the consumption of chicken meat. Overall, the human ESBL-producing *E. coli* prevalence was 0.14% and 0.18% for the SIS model and the SISIR model, respectively (Table 6). The results of the intervention scenarios are given in Figure 6. Overall, interventions that were able to reduce the animal level prevalence at slaughter as described in Section 3.4 were also effective in reducing the prevalence in humans.

4. Discussion

4.1. Transmission dynamics

The models in this study captured the transmission dynamics of ESBL-producing *E. coli* by including various aspects of the infection characteristics as well as the features of the Dutch broiler production chain and evaluated the effects of intervention scenarios. To our knowledge, this is the first study that mechanistically modelled the reported decrease in the ESBL-producing *E. coli* prevalence during a production round (Huijbers et al. 2016; Dierikx et al. 2013; Dame-Korevaar et al. 2017; Laube et al. 2013; Apostolakos et al. 2019). Two models were developed based on two

different assumptions on the prevalence reduction mechanism: time-dependent transmission rate reduction and partial immunity to phylogenetic groups. Some studies reported that the microbiota in chickens changes as they age (Lu et al. 2003; Jurburg et al. 2019; Ballou et al. 2016) and that the development of the microbiota was associated with immune cell activation (Meijerink et al. 2020). Furthermore, antibiotic resistance levels in intestinal *E. coli* decreased as broilers got older (Diarra et al. 2007). We assumed that age-related change in the microbiota influenced the susceptibility of chickens and modelled it as a time-dependent reduction in transmission rate (ψ) using the SIS model. The time-dependent reduction was estimated at 0.69, which implies the transmission is reduced exponentially by 0.69 per time step. More longitudinal studies that focus on the shifts in susceptibility and immunity of chicks are needed to validate this estimated value. Another assumption on the underlying mechanism of the prevalence reduction was made based on the susceptibility differences and partial immunity against phylogenetic groups. As repeated shifts in the phylogenetic group are believed to be the main cause of the persistence of the bacteria in poultry farms (Apostolakos et al. 2019), we used the SISIR model to demonstrate the transmission. To support this assumption, longitudinal research that focusses on the dynamics of phylogenetic groups, including rates of transmission, duration of the infection, and the changes in susceptibility of chickens in all production stages, is needed. Furthermore, an experimental longitudinal study on parent stock birds reported that the type of plasmids might influence the ability of the conjugation process, thus leading to the decline in the prevalence (Dame-Korevaar et al. 2017). More focus might be also needed not only on phylogenetic types but also on the plasmid level.

According to our models, the infectious period was overall shorter and the transmission rate was higher than in the previous study (Huijbers et al. 2016) which was driven by the initial steep increase in the prevalence (Table 5). At slaughter (day 42), the animal level prevalence from both models was lower than 19.1% from the study by Huijbers but more or less consistent with the reported value of 9.8% in Dutch broilers ("Nethmap-MARAN 2021" 2021). Although the reported prevalence might be not comparable because the current model was built on data from an organic farm, the models were still able to capture the transmission dynamics in the broiler production chain. One of the strong points of using data from an organic farm is that it has a long rearing period compared to other conventional farms, which makes more data points available. Furthermore, the number of organic farms is expected to increase in accordance with the current European policy, including the Regulation (EU) 2019/6 and the Farm to Fork strategy, which increases the relevance of our models (European Commission 2018, 2019).

The shifts in animal level prevalence through the production chain were similar to the pattern reported in the modelling study by Plaza et al. (2018). The prevalence started at around 10% in PS farms, dropped in hatcheries, and then increased to the highest in broiler farms. The prevalence of ESBL/AmpC-producing *E. coli* in PS farms in Italy was reported at 92.5% in 1-day-old and 20% in 30-week-old birds (Apostolakos et al. 2019). In Finland, it was reported to be 26.7% in 46-week-old birds. These values are not comparable because the PS farms in our models consisted of different age groups, and further observational study is needed to better understand the transmission dynamics in PS farms. At the hatchery level, the estimated level of egg contamination was within the range of the reported values, which ranged from 0% (Oikarainen et al. 2019) to 3.8% (Mezhoud et al. 2016).

4.2. Intervention scenarios

The influence of the reduction of the shedding and transmission rates was only observed in the SIS model. In this model, exponential transmission rate reduction resulted in a faster reduction in the prevalence, while in the SISIR model, the transmissibility was assumed to be constant and the reduction level was not enough to influence the prevalence. In practice, vaccination or CE can reduce the shedding of bacteria which can then decrease transmission between birds. Even though the effect level is unknown, this can be further explored by combining the first and second scenarios. Administration of CE or vaccination should be done in the early stage of life, as birds started excreting the bacteria within 24 hours after inoculation (Ceccarelli et al. 2017). However, when the shedding rate of the SISIR model was reduced to 1.0×10^{-5}, the prevalence increased unexpectedly. This implies that interventions that slow the spread of the bacteria can increase the

prevalence because a bird needs longer time to become infected and to reach the recovered status. If the transmission dynamics follow the SISIR model, such intervention should not be recommended.

For both models, the most effective control measure can be farm management that aims to reduce the number of bacteria in the environment. Furthermore, the control measure should be applied in combination with biosecurity measures to prevent transmission between stages, as a study suggested that half of the genotypes were originated from the previous stage (Apostolakos et al. 2019). We need to explore cost-effective methods that can be universally applicable to every production stage. The alternative but costly option can be routinely collecting and checking the environmental samples. More quantitative studies on the cost effectiveness of such management and the influence on the public health are expected.

4.3. Sensitivity analysis

In the SIS model, the animal level prevalence within broiler flocks was sensitive to parameters that determined the duration of infection (γ) and the reduction of transmission (ψ). In contrast, these parameters did not influence the prevalence at the flock level, because outbreaks can still occur from the influx from the hatcheries or through the environmental contamination from previous production rounds. The flock level prevalence did decrease with the bacteria survival in the environment (ρ) and pseudo vertical transmission rate (l), indicating that reducing these factors is important for controlling the bacteria at a national level. In the SISIR model, both animal and flock level prevalence in broiler farms were sensitive to the parameters that determined the duration of infection (γ_1), pseudo vertical transmission (l), and colonization at hatching (m). Both models indicated that controlling the duration of infection of broilers as well as the contamination level of eggs are the main options to be explored to reduce the spread of bacteria.

4.4. Quantitative Microbiological Risk Assessment

According to the SIS and SISIR model, the ESBL-producing *E. coli* prevalence in humans due to chicken consumption was only 0.14% and 0.18%, respectively (Table 6). Considering the prevalence in the general Dutch population, which was reported to be around 5.0% to 8.6% (Reuland et al. 2016; van den Bunt et al. 2019), chicken meat consumption can still be considered a minor contribution to human exposure at around 1.6% to 3.6%. Our estimate is comparable to the epidemiological study that estimated that chicken meat accounted for 4.5% of intestinal carriage of ESBL or pAmpC gene in the general population (Mughini-Gras et al. 2019). We used the animal level prevalence at slaughter as the fresh chicken meat prevalence which was 10.6% and 13.6%, respectively. These values were much lower than the reported value of 67.0% (Evers et al. 2017) and thus might have underestimated the risk. However, considering the recent downward trend in prevalence in broilers, the values used in this study can be regarded as relevant enough. We ignored the effect on prevalence from the slaughter process because even though the process reduced bacteria concentration, it seemed to have little effect on prevalence (Pacholewicz et al. 2015). As a previous study revealed that the gene distribution in chicken meat at retail was distant from that of broilers and chicken meat at the slaughterhouse (Dorado-García et al. 2018), an investigation on cross-contamination is needed to better understand the possible source of human exposure.

4.5. Limitations

The main limitation of this study is that the model was fitted using only one observational study on an organic broiler farm. Although not enough longitudinal studies are available and almost no study investigated the infection dynamics of the phylogenetic groups, we were able to mimic the prevalence observed in the Netherlands. Still, we recommend future studies focus on these issues.

Our model assumed that one farm consisted of one flock and did not include transmission between flocks within the same farm or the effect of spatial separation on between-farm transmission, both of which were identified as transmission routes in a previous study (Dame-Korevaar, Fischer, van der Goot, Stegeman, et al. 2019). In addition, further study could also include the difference in farm size and the seasonal effect.

Uncertainty around parameter values is also one of the weaknesses of this study. The uniform prior distributions chosen for the ABC method might be too large, which might have an impact on the rejection of the appropriate value at the early stage. The availability of the data on vertical transmission should also be addressed in future studies. The pseudo vertical transmission rate was set at 0.009, which was the proportion of contaminated eggs before and after disinfection from a previous study (Projahn et al. 2017). The same study reported that 1.1% of the hatchlings were colonized with enterobacteria and we used the value as the hatching colonization rate (*m*). However, this study reported that disinfection of eggs decreased the prevalence from 1.8% to 0.4% and another study reported that the prevalence in disinfected eggs was reduced from 1.3% to 0% after incubation (Oikarainen et al. 2019). We might have set both rates too high, resulting in an overestimation of transmission. This overestimation might have led to the higher prevalence in the broiler farms which implies that the risk to human health might even be lower.

There are several limitations specific to the SISIR model. It is highly unlikely that an animal would get immunity after two infections. Considering the infection duration and the variance in phylogenetic groups, at least three or four infections should occur during the production cycle in broilers and even more for PS birds. The major phylogenetic groups found in the study by Huijbers were A and B1 as was also the case in other reports (Zurfluh et al. 2014; Ewers et al. 2021). We assumed that the constitution of the phylogenetic groups was the same throughout the production chain, although a study has pointed out that it can differ among the stage (Apostolakos et al. 2019). To improve the model, it might be an option to incorporate more phylogenetic groups or add a time-related immunity decrease. Although at the same time it will make the modelling more complex, resulting in the increased assumptions due to data unavailability and difficulties in translating the results (Katsma et al. 2007).

5. Conclusions

We developed transmission models of ESBL-producing *E. coli* in the Dutch broiler production chain based on two different mechanisms of acquiring immunity and assessed the effect of control measures. Furthermore, the effect of mixing birds and eggs from different origins and the number and size of flocks were also considered to capture the transmission throughout the production chain. Both models were able to describe the observed dynamics equally well and estimate the outcomes of the interventions quantitatively. Both indicated that improving farm management to eliminate the bacteria from the environment is the most effective intervention, which makes the influence of the intervention on the outcomes robust. According to our models, transmission to humans from contaminated chicken meat was not the major risk factor. Although contribution of chicken meat to human prevalence is limited, it is still important to monitor ESBL-producing *E. coli* and try to reduce them as much as possible because they can serve as the source of antimicrobial resistance genes.

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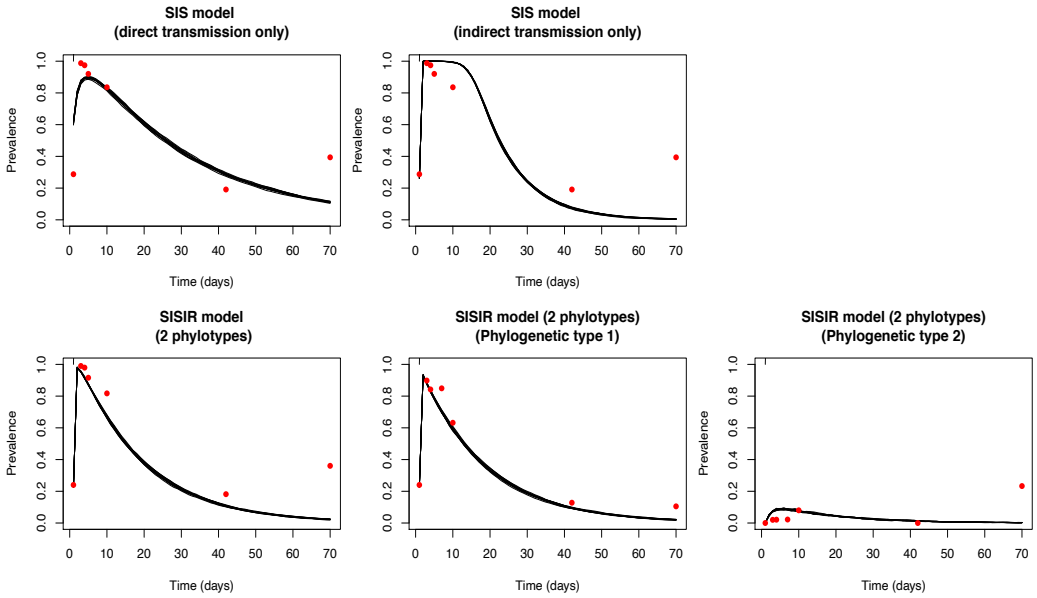
8. Supplementary information



S1. *ABC-simulated prevalence (black line) and observed data (red points). Top left: SIS model with only direct transmission. Top middle: SIS model with only indirect transmission. Bottom left: SISIR model with 2 phylogenetic types. Bottom middle & right: Specific phylogenetic groups in the SISIR model.*

S2. *Prior distributions and medians of the posterior distribution of the parameters.*

Parameter	**Prior distribution**	**Posterior distribution (95% CI)**		
		SIS model (direct)	**SIS model (indirect)**	**SISIR model (2 phylotype)**
β1	Uniform (0, 10)	2.42 (1.08, 5.27)	-	-
β2	Uniform (0, 10)	-	4.20 (0.23, 9.51)	-
$\beta2_1$	Uniform (0, 10)	-	-	5.05 (0.43, 9.66)
$\beta2_2$	Uniform (0, 10)	-	-	4.58 (0.38, 9.67)
ψ	Uniform (0, 1)	0.34 (0.07, 0.77)	0.67 (0.28, 0.97)	-
γ	Uniform (0, 1)	0.03 (0.01, 0.11)	0.10 (0.02, 0.21)	-
γ_1	Uniform (0, 1)	-	-	0.06 (0.02, 0.10)
γ_2	Uniform (0, 1)	-	-	0.49 (0.06, 0.96)
Θ	Uniform (0, 1)	-	0.55 (0.04, 0.96)	0.49 (0.04, 0.96)
ρ	Uniform (0, 1)	-	0.51 (0.06, 0.97)	0.52 (0.04, 0.97)

SIS model (direct): SIS model with direct transmission with time-dependent transmission reduction. SIS model (indirect): SIS model with indirect transmission with time-dependent transmission reduction. SISIR model (2 phylotype): SISIR model with two phylogenetic groups. β1: Direct transmission rate for the SIS model. $\beta2_i$: Indirect transmission rate. *i* denotes phylogenetic type *i* in the SISIR model.ψ: transmission reduction. γ_i: Recovery rate. *i* denotes phylogenetic type *i* for the SISIR model. θ: Bacterial shedding rate. ρ: Bacteria survival rate in the environment.

S3. *Simulated animal-level prevalence at slaughter time with interventions and human prevalence due to consumption for the SIS and SISIR model.*

Intervention	**SIS model**		**SISIR model**	
	At slaughter	Human	At slaughter	Human
1-i	5.60 (5.30, 5.88) ±0.93 (0.20, 1.64)	0.08(0.07,0.08)±0.00	14.03 (12.94, 14.73) ±1.88 (1.19, 4.09)	0.19 (0.17, 0.20) ±0.01
	96.15 (92.31, 100) ±4.05		98.46 (92.31, 100.00) ±3.24	
1-ii	3.51 (3.28, 3.82) ±1.08 (0.22, 1.50)	0.05(0.04,0.05)±0.00	14.19 (13.27, 15.07) ±1.55 (1.09, 3.52)	0.19 (0.18, 0.20) ±0.01
	90.77 (84.62, 100) ±6.07		99.23 (94.04, 100) ±2.43	
1-iii	0.00(0.00, 0.00) ±0.00(0.00, 0.02)	0.00(0.00,0.00)±0.00	20.83 (19.51, 21.45) ±3.14 (1.94, 5.73)	0.28 (0.26, 0.29) ±0.01
	0.77 (0.00, 5.96) ±2.43		99.23 (94.04, 100) ±2.43	
2-i	10.13 (9.98, 10.21) ±0.28 (0.22, 0.33)	0.14(0.13,0.14)±0.00	13.88 (12.78, 14.47) ±1.84 (1.15, 4.05)	0.19 (0.17, 0.19) ±0.01
	100.00 (100.00, 100.00) ±0.00		98.46 (92.31, 100) ±3.24	
2-ii	9.17 (8.66, 9.33) ±0.55 (0.27, 2.09)	0.12(0.12,0.13)±0.00	14.03 (12.45, 14.83) ±1.73 (1.23, 4.55)	0.19 (0.17, 0.20) ±0.01
	99.23 (94.04, 100.00) ±2.43		98.46 (88.08, 100.00) ±4.87	
2-iii	1.58 (1.28, 1.88) ±0.72 (0.44, 0.89)	0.02(0.02,0.03)±0.00	14.20 (13.28, 14.88) ±1.53 (1.13, 3.49)	0.19 (0.18, 0.20) ±0.01
	88.46 (76.92, 100.00) ±8.31		99.23 (94.04, 100.00) ±2.43	
3-i	10.60 (10.04, 10.84) ±0.59 (0.26, 2.41)	0.14(0.13,0.15)±0.00	13.83 (12.87, 14.35) ±1.86 (1.07, 4.11)	0.19 (0.17, 0.19) ±0.01
	99.23 (94.04, 100.00) ±2.43		98.46 (92.31, 100.00) ±3.24	
3-ii	10.60 (10.06, 10.82) ±0.60 (0.24, 2.42)	0.14(0.14,0.15)±0.00	14.66 (14.2, 15.23) ±1.28 (1.17, 1.4)	0.20 (0.19, 0.20) ±0.00
	99.23 (94.04, 100.00) ±2.43		100.00 (100.00, 100.00) ±0.00	
3-iii	0.65 (0.00, 1.44) ±2.15 (0.00, 3.79)	0.01(0.00,0.02)±0.01	0.71 (0.00, 1.79) ±2.33 (0.00, 4.68)	0.01 (0 .00, 0.02) ±0.01
	6.15 (0.00, 13.65) ±4.87		5.38 (0.00, 13.65) ±5.19	
3-iv	1.23 (0.00, 1.67) ±3.09 (0.00, 4.07)	0.02(0.00,0.02)±0.01	0.75 (0.00, 2.00) ±2.43 (0.00, 5.12)	0.01 (0.00, 0.03) ±0.01
	11.54 (0.00, 15.38) ±6.54		5.38 (0.00, 13.65) ±5.19	
4-i	0.15 (0.00, 0.74) ±0.53 (0.00, 2.72)	0.00(0.00,0.01)±0.00	0.60 (0.00, 1.02) ±2.18 (0.00, 3.72)	0.01 (0.00, 0.01) ±0.01
	1.54 (0.00, 7.69) ±3.24		4.62 (0.00, 7.69) ±3.97	
4-ii	0.61 (0.00, 1.51) ±1.85 (0.00, 3.69)	0.01(0.00,0.02)±0.01	0.52 (0.00, 1.16) ±1.86 (0.00, 4.12)	0.01 (0.00, 0.02) ±0.01
	6.15 (0.00, 15.38) ±6.07		3.85 (0.00, 7.69) ±4.05	

Top row: Mean animal-level prevalence in % (95% CI) ± SD (95% CI). Bottom row: flock-level prevalence in % (95% CI) ± SD. The 95% CI of the mean prevalence shows the range over iterations. The SD shows the variation between flocks within the simulation. The 95% CI of the SD shows the variation between the iterations. Intervention 1: Reduction of shedding rate (PS and broilers), (i) 1.0×10^{-2}, (ii) 1.0×10^{-3}, (iii) 1.0×10^{-5}. Intervention 2: Reduction of direct/ indirect transmission rate (PS and broilers), (i) 0.7, (ii) 0.3, (iii) 1.0×10^{-3}. Intervention 3: Decreasing bacteria survival rate during the vacancy period (Broilers), (i) 0.5, (ii) 0.25, (iii) 1.0×10^{-2}, (iv) 0. Intervention 4: Decreasing bacteria survival rate (PS and broilers), (i) 1.0×10^{-2}, (ii) 0.