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Extended spectrum cephalosporin (ESC) resistant *Escherichia coli*: Trends and seasonality in the Netherlands from 2014 to 2022

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ABSTRACT

Background: Antimicrobial resistance (AMR) in livestock and the environment likely contribute to the prevalence of AMR in humans with potential detrimental effects on human health. As such, annual mandatory monitoring of AMR in livestock occurs within the European Union (EU), according to harmonised methods. Extended-spectrum cephalosporins-resistant (ESC-resistant) *Escherichia coli*, including extended-spectrum β-lactamases (ESBL), AmpC β-lactamases (AmpC) and carbapenemase producing *E. coli*, are considered of particular importance and are therefore included in the monitoring program.
Methods: Using results from the annual monitoring of ESC-resistant *E. coli* from 2014–2022, trends in prevalence per animal sector were determined over the complete time period, as well as potential seasonal effects.
Results: During these nine years, significant changes were observed in the prevalence of ESC-resistant *E. coli*, in broilers, dairy cattle and veal calves, while no changes in prevalence were seen in slaughter pigs. Furthermore, the prevalence of ESC-resistant *E. coli* is positively correlated with warmer seasons (summer and autumn) for both dairy cattle and veal calves, while no associations were found for broilers and slaughter pigs. While temperature itself may play a role in the prevalence of ESC-resistant *E. coli*, other factors affecting the selective landscape, such as antibiotic usage, will also play a role.
Conclusion: A combined analysis of antimicrobial usage and prevalence of ESC-resistant *E. coli* through the year, both in livestock and human samples, would be an interesting follow-up of this study.

1. Introduction

The challenge that antimicrobial resistance (AMR) poses for human healthcare has been recognised for a long time, and in most regions of the world, efforts to reduce the spread of antimicrobial resistant bacteria are made [1]. The abundant use of antimicrobials in human and veterinary medicine, growth promotion in livestock and agricultural usage has selected for an increase of resistance, both through vertical transmission of resistant organisms and horizontal spread of acquired AMR-genes on mobile genetic elements. Furthermore, transmission of antimicrobial residues into the environment causes increased selective pressure outside of the intended field, creating a true One Health problem that is ubiquitously present on a global scale [2].

Cephalosporins, specifically of the third and fourth generation, have been developed to act on a broad spectrum of Gram-negative bacteria, and are referred to here as extended-spectrum cephalosporins (ESCs). ESCs are part of the highest priority of clinically important antimicrobials (CIA) for human healthcare and resistance against these antimicrobials in Gram-negative bacteria is often monitored through the presence of ESC-

Abbreviations: AMR, antimicrobial resistance; EU, European Union; ESCs, extended-spectrum cephalosporins; ESC-resistant, extended-spectrum cephalosporins-resistant; ESBL, extended-spectrum β-lactamases; AmpC, AmpC β-lactamases; CIA, clinically important antimicrobials; WHO, World Health Organization; EFSA, European Food Safety Authority; MARAN, Monitoring of antimicrobial resistance and antibiotic usage in animals in the Netherlands; LOESS, locally estimated scatterplot smoothing; KNMI, Royal Netherlands Meteorological Institute; ACF, autocorrelation function.

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resistant *Escherichia coli*, as these bacteria are easy to culture, universally present in the gut of terrestrial animals and are generally accepted as representative of the presence of AMR encoding plasmids in bacterial populations [3]. Genotypically, ESC-resistance in *E. coli* can be attributed to the presence of extended-spectrum β-lactamases (ESBL), plasmid-mediated AmpC β-lactamases (*ampC*) genes, or chromosomal mutations in the *ampC* promotor region that induce hyper-production of the wildtype AmpC [4].

As part of the Global Action Plan on AMR, the World Health Organization (WHO) recommends an integrated surveillance protocol entitled the "Tricycle protocol" to enable monitoring of ESC-resistant *E. coli* for humans, livestock and the environment at national, regional and international levels [3]. Within the EU, such surveillance has been mandatory for food-producing animals since 2014 under implementing Decision 2013/652/EU [5]. These data are summarised at European Union (EU) level by the European Food Safety Authority (EFSA) based on the data that is provided by the EU member states [6]. The data is summarised per year by certain countries at national level [7]. For the Netherlands, these results are reported yearly in the Monitoring of antimicrobial resistance and antibiotic usage in animals in the Netherlands (MARAN) report [8].

Analyses to compare the trends in resistance data for randomly isolated *E. coli* from livestock in the period of 1998–2016 were previously presented, in which a correlation is indicated between the significant reduction in resistance for several antimicrobial classes with a reduction in the usage of those antimicrobials [9]. In this study, we aimed to analyse data from the monitoring on antimicrobial resistance in livestock in the Netherlands for selectively isolated ESC-resistant *E. coli,* assessing trends and seasonality over nine years (2014–2022).

2. Materials and methods

ESC-resistant *E. coli* were selectively isolated from faecal samples of livestock as described by the EU Reference Laboratory for AMR [10]. The prevalence of ESC-resistant *E. coli* per livestock species between 2014–2022 was analysed from the raw data as reported in MARAN 2023 [8]. One caecal sample was analysed per flock, prevalence and number of samples analysed per year are described in Supplementary material 2 (Table S1).

A time-series study was performed on the frequency of ESC-resistant *E. coli* in five different animal production sectors in the Netherlands: broilers, pigs, dairy cattle, rosé veal calves and white veal calves. The time series analysis used a time interval of one season: Q1) March, April, and May (Spring); Q2) June, July, and August (Summer); Q3) September, October, and November (Autumn); and Q4) December, January, and February (Winter). The time series were first visually inspected to observe trends and possible seasonality during the nine-year period on the frequency of ESC-resistant *E. coli*. The dispersion of the temporal data was smoothed using locally estimated scatterplot smoothing (LOESS) as implemented in library 'ggplot2' in *R* [11]. For descriptive purposes we gathered data on the average monthly temperature, calculated based on the daily mean temperature in De Bilt in the Netherlands, which were downloaded from the archive of the Royal Netherlands Meteorological Institute (KNMI) [12] and averaged by season.

Generalized linear models were used, employing a log link and a Poisson distribution, i.e., time series regression models [13,14]. The models were specified using the time as trend (i.e., 36 intervals resulting from nine years split into four seasons), and the seasons as a categorical variable in the fixed effects. For rosé and white veal calves, and for broilers, the visualization of ESC-resistant *E. coli* distribution over time leads to observed changes in the trend during the period 2014–2022. This was taken into account by including an interaction term in the model for the change in the direction of the trend after 2020, 2016, and 2017 for broilers, veal calves rosé and white, respectively.

Differences on the frequency of ESC-resistant *E. coli* in the different seasons was tested using the detrended time series with the classic Wald test, employing an approximation by the chi-square distribution, as implemented in *R* routine 'Anova' from the 'car' library [15]. This was followed up by pairwise comparisons made with a Bonferroni controlling for experiment wise error, as implemented in *R* routine 'emmeans' from library 'emmeans' [16]. The models' adequacy is available in the supplementary material 1, and was assessed visually from an autocorrelation function (ACF) plot and using the Breusch–Godfrey test for serial correlation as implemented in *R* routine 'check_residuals' from library 'forecast', and overdispersion as implemented in the *R* routine 'check_overdispersion' from library 'performance' [17,18]. The descriptive analysis and the model were implemented in *R* [19].

3. Results

Based on publicly available data off weather trends in the Netherlands from 2014 to 2022, the year was divided into four seasons, spring, summer, autumn and winter, and the average prevalence of ESC-resistant *E. coli* was calculated (Fig. 1). Results of the regression analysis determining the trends over the years and differences between seasons are presented in Table 1.

For broilers, there is an obvious reduction from 66 % in 2014 to 10 % in 2020, followed by a small increase to 15 % in 2022 (Fig. 1). Indeed, a significant reduction of on average 6.8 % per quarter of a year was measured in the first period (2014–2020), followed by an average increase of 3.5 % in the second period (2021–2022) (Table 1). When analysing the effects of the seasons on broilers, no significant correlation between season and ESC-resistant *E. coli* prevalence was measured (Table 1, Fig. 2).

ESC-resistant *E. coli* from slaughter pigs have been isolated at similar rates throughout the whole study period, without much fluctuation. Seasons also appear to have no influence on the frequency at which ESC-resistant *E. coli* are isolated.

The frequency at which ESC-resistant *E. coli* are isolated is the lowest in dairy cattle. Over the period from 2014 to 2022, a significant increase of on average 1.4 % per quarter of a year was detected. Furthermore, a significant difference in average prevalence is measured between the summer and autumn seasons, which are predicted by the model at ∼20 % versus ∼5 % in the winter and spring seasons.

In the Netherlands, veal calves can be discriminated into two populations based on management practices, referred to as white and rosé veal calves. As antimicrobial usage in these populations differ, they are generally reported separately [20]. In both populations, a significant increase was measured, followed by a reduction (Table 1). For rosé veal calves, there was a significant increase of on average 10.7 % per quarter of a year from 2014 to 2016, followed by a significant reduction of on average 1.3 % between 2017 and 2022. In the white veal calves, the significant increase was an average of 7.1 % per quarter of a year from 2014 to 2017, followed by a significant reduction of on average 1.8 % between 2018 and 2022. In both sectors of veal calves, a significant difference is measured in the model for the seasons (Table 1). In rosé veal calves, this prevalence was ∼49 % in summer and autumn versus ∼19 % in winter and spring. In white veal calves, this was ∼61 % in summer and autumn versus ∼39 % in winter and spring.

4. Discussion

ESC-resistant *E. coli,* including those possessing both ESBL and AmpC-related mechanisms, are viewed as one of the most relevant bacteria for monitoring of AMR in a One Health setting, encompassing humans, livestock, food and the environment. In the Netherlands, ESC-resistant *E. coli* have been monitored selectively in livestock since 2014. In this study, these data from 2014 to 2022 were analysed to assess the trends over time, including seasonality, of ESC-resistant *E. coli* for different livestock sectors.

The prevalence of ESC-resistant *E. coli* in broilers in the Netherlands was much higher before 2010 when different policies were in place concerning antibiotic usage, although selective monitoring has only been

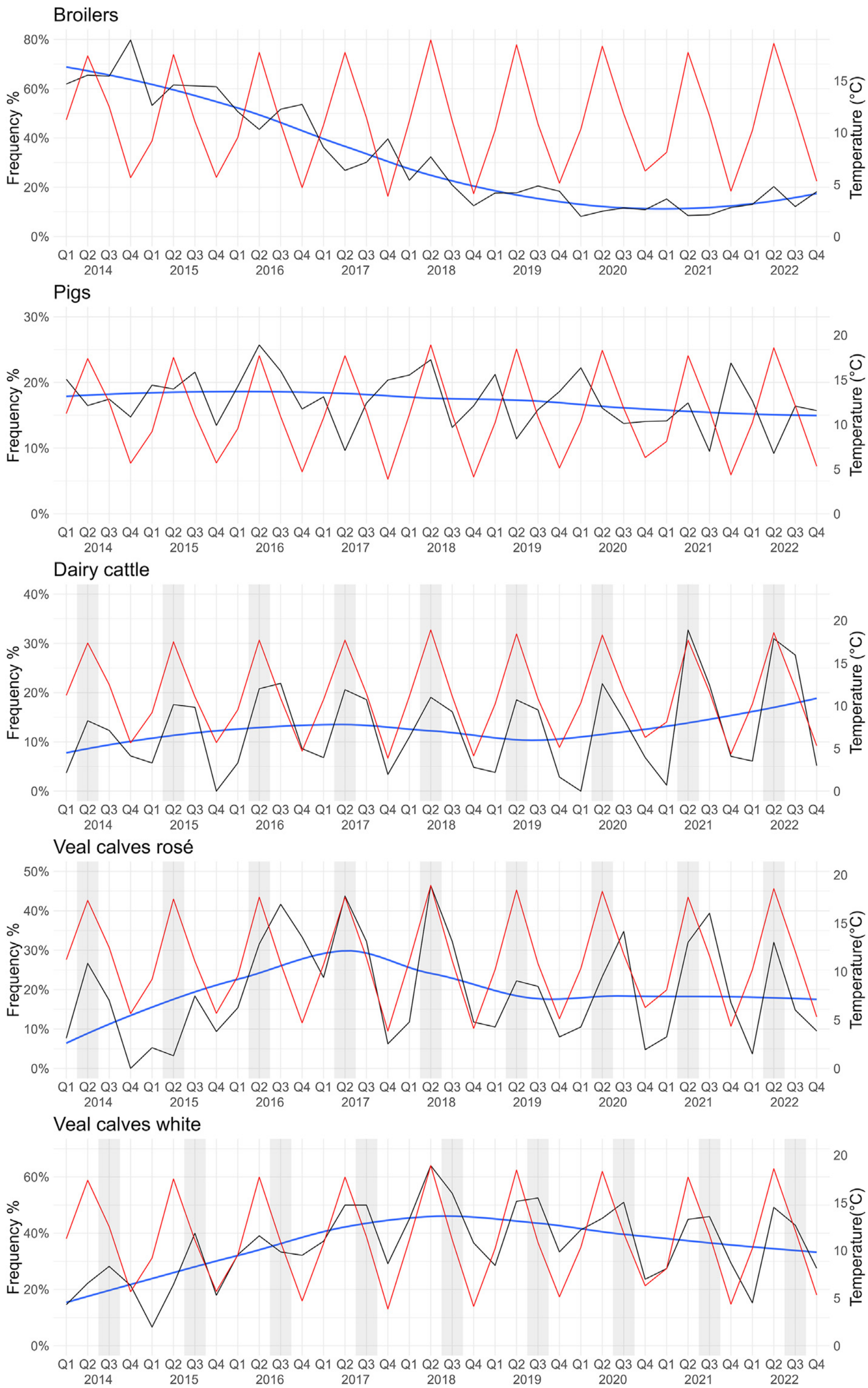

Fig. 1. Descriptive temporal distribution of the relative frequency (%) of ESC-resistant *Escherichia coli* (black line) in the Netherlands between 2014 and 2022. The primary y-axis and black line show the frequency of ESC-resistant *E. coli* per season between 2014 and 2022 in the Netherlands in five productive sectors: broilers, pigs, dairy farms, veal calves rosé and veal calves white. The blue line is the smoothed average over years. The red line and secondary y-axis show the average temperature (°C) in each season. Q1: March, April, and May (Spring); Q2: June, July, and August (Summer); Q3: September, October, and November (Autumn); and Q4: December, January, and February (Winter).

in place since 2014 [21,22]. While this reduction was previously shown for non-selectively isolated ESC-resistant *E. coli*, here the reduction is confirmed using a selective isolation strategy, which is now recommended for monitoring purposes [3,9]. Furthermore, the model that was used in this study indicates an increase in the prevalence of ESC-resistant *E. coli* in broilers in the period between 2021 and 2022.

This increase was probably caused by a change in the sampling strategy in the mandatory EU monitoring, where individual broilers within a flock were sampled until 2021, and a pooled sample of caecal content of 10 broilers per flock was used in 2022 [10]. We hypothesize that the process of pooling animals for sampling results in an increase of sensitivity in the ESC-resistant *E. coli* detection. Assuming that within a batch the broilers have similar probability of being ESC-resistant *E. coli* positive, the probability of a sample being positive increases directly with the number of pooled animals in the sample, according to an hypergeometric distribution (i.e., increase of the batch sensitivity) [23].

The prevalence of ESC-resistant *E. coli* has always been relatively low at dairy farms in the Netherlands (approximately 10 %), and few studies have been published in which this sector was thoroughly investigated [24,25]. Although the prevalence in dairy cattle is still relatively low (below 20 % during the whole time-series), the increasing trend over the years is surprising (Fig. 1, Table 1), and is unexplained at this time as

Table 1
Regressions analyses based on a generalised linear model to determine ESC-resistant *Escherichia coli* (ESC-R) antimicrobial resistance prevalence (%) trends and seasonality between 2014 and 2022 in the Netherlands.

Species	Variable	Coefficient (*SE*)	ESC-R/% ([a],[b])	*P* value
Broilers	Intercept	−0.276	–	–
	Trend 2014–2020	−0.070 (0.046)	−6.80	< 0.001
	Trend 2021–2022	0.104 (0.048)	3.50	0.032
	Spring (Q1)	–	12.30	0.530
	Summer (Q2)	0.100 (0.080)	13.40	
	Autumn (Q3)	0.170 (0.090)	14.70	
	Winter (Q4)	0.310 (0.480)	17.00	
Pigs	Intercept	−1.550	–	–
	Trend 2014–2022	−0.006 (0.004)	−0.68	0.130
	Spring (Q1)	–	18.80	
	Summer (Q2)	0.100 (0.080)	16.30	
	Autumn (Q3)	0.170 (0.090)	16.10	0.140
	Winter (Q4)	0.310 (0.480)	17.10	
Dairy cattle	Intercept	−3.100		–
	Trend 2014–2022	0.010 (0.005)	1.40	0.010
	Spring (Q1)	–	5.50 (a)	< 0.001
	Summer (Q2)	1.400 (0.190)	22.00 (b)	
	Autumn (Q3)	1.200 (0.190)	18.00 (b)	
	Winter (Q4)	−0.100 (0.240)	4.90 (a)	
Rosé veal	Intercept	−3.100	–	–
	Trend 2014–2016	0.100 (0.020)	10.70	< 0.001
	Trend 2016–2022	−0.110 (0.030)	−1.30	< 0.001
	Spring (Q1)	–	19.10 (a)	< 0.001
	Summer (Q2)	0.940 (0.230)	49.30 (b)	
	Autumn (Q3)	0.950 (0.230)	49.50 (b)	
	Winter (Q4)	0.019 (0.310)	19.50 (a)	
White veal	Intercept	−2.100	–	–
	Trend 2014–2017	0.070 (0.010)	7.10	< 0.001
	Trend 2017–2022	−0.080 (0.010)	−1.80	< 0.001
	Spring (Q1)	–	40.00 (a)	< 0.001
	Summer (Q2)	0.420 (0.110)	61.00 (b)	
	Autumn (Q3)	0.430 (0.110)	62.00 (b)	
	Winter (Q4)	−0.040 (0.130)	38.00 (a)	

[a] For trends, it represents the percentage variation on ESC-resistant *E. coli* prevalence per quarter of the year. For the season, it represents the ESC-resistant *E. coli* prevalence per season and the *P* value from the detrended time series.
[b] Letters 'a' and 'b' represent different outcomes of the model at the significance level of 0.05; pairwise comparisons correcting with Bonferroni correction for multiple comparisons. Abbreviations: ESC, extended spectrum cephalosporin; *SE*, standard error.

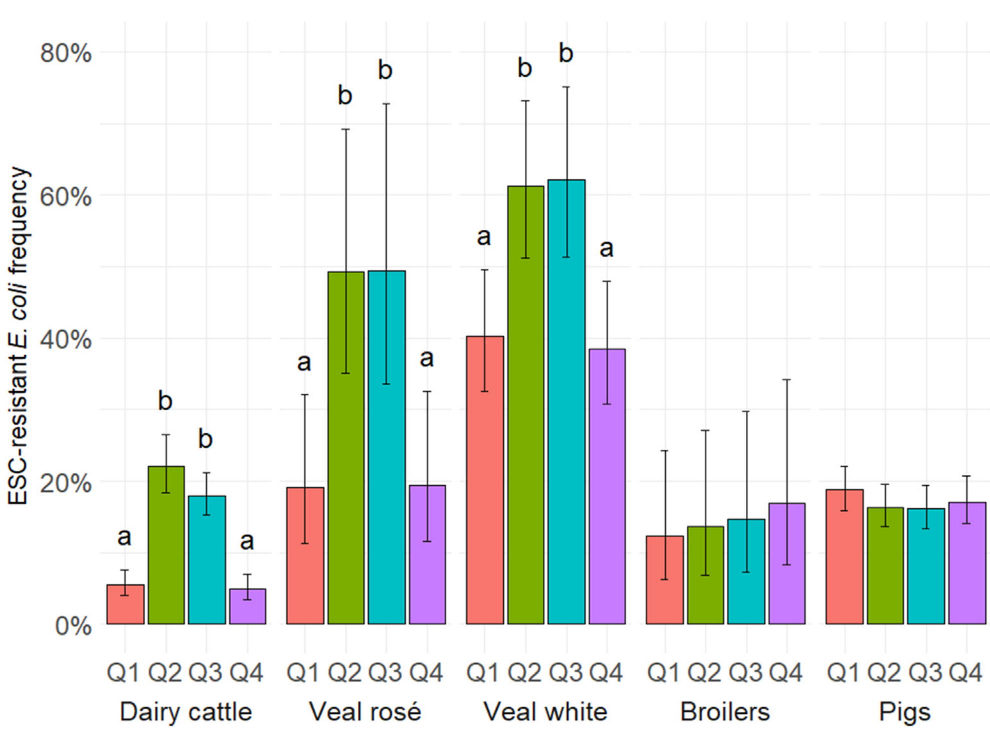

Fig. 2. ESC-resistant *Escherichia coli* frequency per season and sector between 2014 and 2022 in the Netherlands. Percentage per season averaged over the complete study period and the *P* value from the detrended time series. Letters 'a' and 'b' represent different outcomes of the model with statistical difference at the significance level of 0.05 obtained via pairwise comparisons correcting with Bonferroni correction for multiple comparisons. Q1: March, April, and May (Spring); Q2: June, July, and August (Summer); Q3: September, October, and November (Autumn); and Q4: December, January, and February (Winter).

antibiotic usage in this sector is low and includes no third and fourth generation cephalosporins [26]. If this increase persists over several years, it will be vital to study which underlying factors contribute to this increase.

In contrast to the dairy sector, in veal calves an increasing trend for ESC-resistant *E. coli* was detected both in rosé and white veal calves several years earlier, although this increase is currently also unexplained [27]. Nonetheless, prevalence has been decreasing again for both populations over the second half of the study period.

The sector of slaughter pigs is the only sector in which no significant trends were detected in the current study period, remaining always stable below 20 %. Each of the livestock systems described here is differently arranged in the Netherlands in terms of pastoral access, biosecurity and arrival of animals, length and arrangement of production cycles, management of airflow in stables and antimicrobial usage, and it is difficult to speculate which of these factors contribute to the trends in ESC-resistant *E. coli* prevalence in these sectors.

The second focus of the current study was to determine if seasonality could be detected from the dataset. So far, seasonality or temperature effects have been detected for ESBL-producing *E. coli* and *Klebsiella* in humans in German and Swiss hospitals, as well as in the general human population in the Netherlands, all of which indicated a positive correlation between a rise in temperature and prevalence of ESBL-producing *E. coli* [28–30]. However, a study in wastewater treatment plants in Germany found a negative association in which a reduced number of ESBL-producing *E. coli* were detected in the summer [31].

For this study, the year was divided into four quarters based on the average temperature per month for this analysis, see Supplementary material 2 (Table S2). No significant seasonal effects were detected for broilers and slaughter pigs. In dairy cattle, rosé and white veal calves, a determined seasonal pattern was detected in which a peak in prevalence of ESC-resistant *E. coli* was observed in summer and autumn compared to winter and spring. While the average temperature in spring and autumn are similar, the differences in ESBL prevalence between these seasons may be caused by a delayed effect from the warmer summer season, similar to the results described by Bock et al. [29]. The presence or absence of seasonality in different types of livestock may lie in the types of stables that are used. Both for poultry and pigs in the Netherlands, the temperature in stables is more tightly regulated than in the dairy and veal farms, and for dairy cattle it is most common that animals graze in pastures in warming temperatures.

While the air temperature is considered in most studies mentioned above, other factors may play a role in the observed seasonality of ESC-resistant *E. coli* prevalence in dairy cattle and veal calves, for which antimicrobial usage is the most obvious. Antimicrobial usage data in livestock animals in the Netherlands is publicly available per year, but not per month or season. It would be valuable for a future study to determine if the seasonal trends for ESC-resistant *E. coli* prevalence that were observed in this study are correlated with any trends over the seasons in antimicrobial usage and prevalence of specific infections in the veal and dairy sectors. Furthermore, the data for other antimicrobial resistant bacteria in livestock could be combined with seasonal antimicrobial usage data in a similar analysis as described in the current study, in order to see if other resistant organisms display similar trends in prevalence.

CRediT authorship contribution statement

Michael S.M. Brouwer: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Eduardo de Freitas Costa:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Anita Dame-Korevaar:** Writing – review & editing, Investigation, Formal analysis. **Adam P. Roberts:** Writing – review & editing, Investigation, Funding acquisition. **Kees T. Veldman:** Writing – review & editing, Methodology, Investigation, Funding acquisition.

Data availability statement

Annual aggregated data are available in the Nethmap/MARAN report at www.wur.nl/maran.

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Declaration of competing interest

Michael S.M. Brouwer is the editorial board member of *Science in One Health*. We have no other competing interests to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.soh.2024.100083.

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