Trends in Antibiotic Resistance in *Salmonella* Isolates from Pigs and Cattle

A. Minter[1], H. Jones[1], S. Harris[2], A. Parry[2], R.P. Smith[1], M. Velasova[1]

[1]Animal and Plant Health Agency – Weybridge, UK, [2]Royal Veterinary College – UK, MSc students

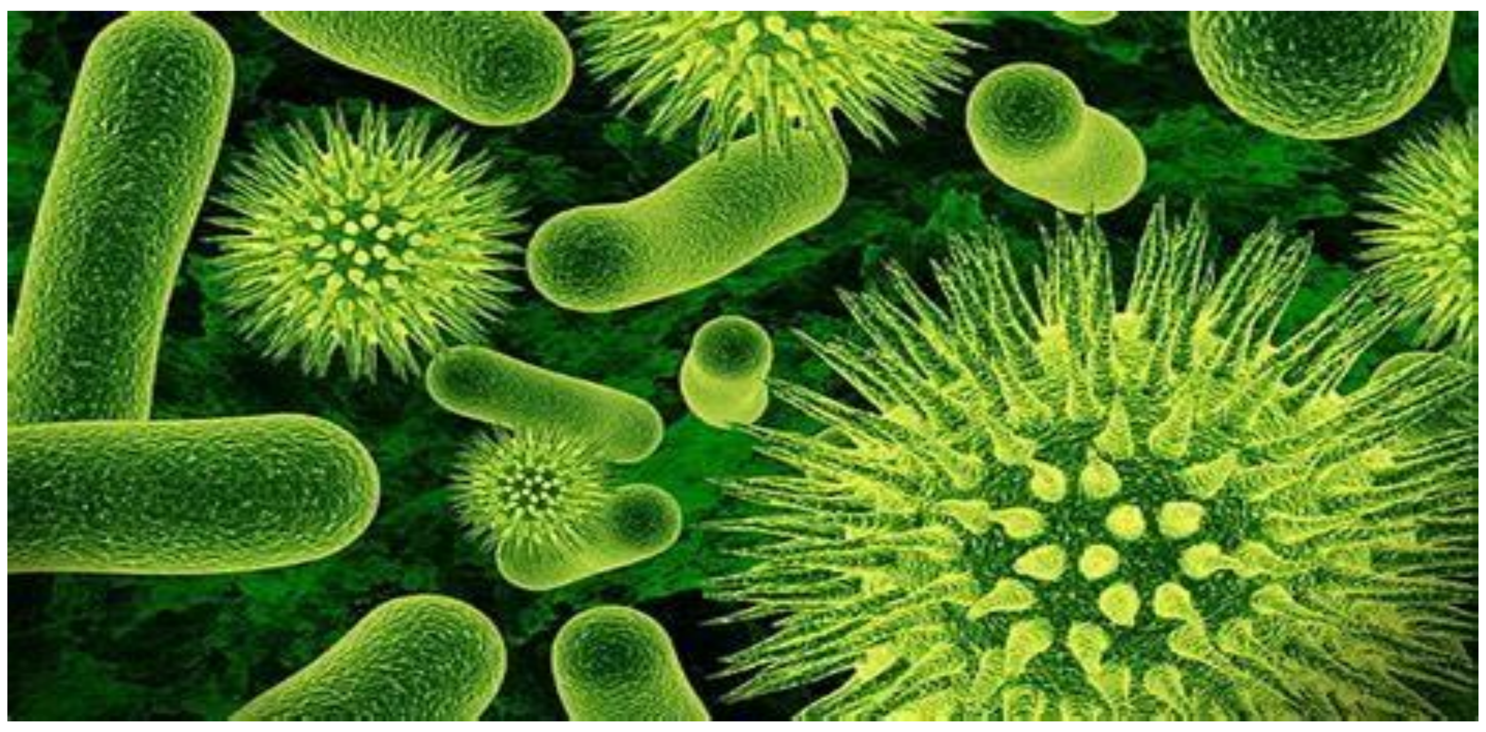
Background

The World Health Organisation (WHO) has classified antimicrobial resistance (AMR) as "one of the top 10 global public health threats facing humanity" (WHO, 2020). Humans can be exposed to resistant bacteria in many ways, including through animal derived food products and agricultural waste (WHO, 2015). The use of antimicrobials in human medicine and livestock production is contributing to the acquisition of resistance (WHO, 2015). Urgent multisectoral action is required (WHO, 2020) and a better understanding of the trends in AMR is essential to controlling the problem.

The objective of this study was to use clinical scanning surveillance data to describe trends in AMR in *Salmonella* isolates originating from pigs and cattle in England and Wales from 2010 to 2020.

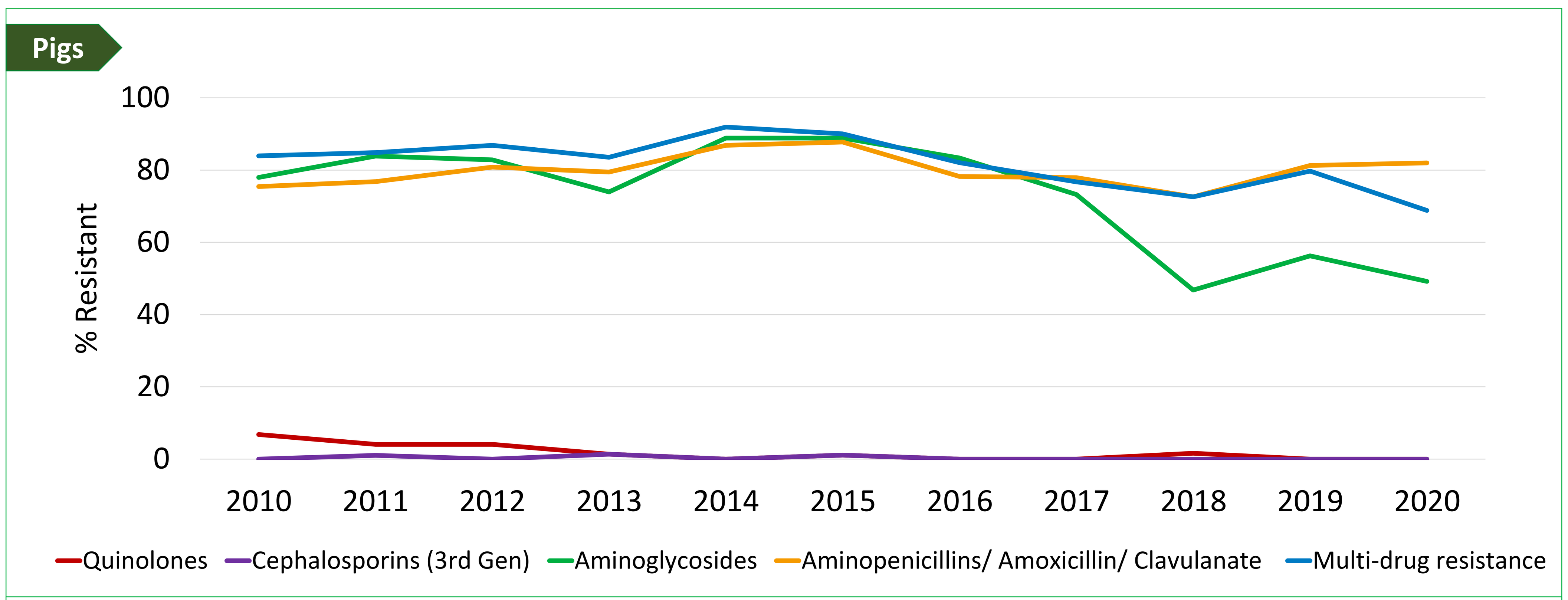
Methods

- The dataset was obtained via the clinical scanning surveillance programme operated in England and Wales by the APHA
- The initial dataset comprised of 1,590 pig Salmonella isolates and 5,952 cattle Salmonella isolates derived from clinical or post-mortem samples submitted by veterinarians for diagnostic testing from 2010 to 2020.
- Isolates were tested for susceptibility to a panel of 16 antimicrobials at APHA laboratories in Weybridge, Lasswade and Penrith, and for susceptibility to enrofloxacin and cefpodoxime at APHA regional laboratories.
- Testing was carried out using disc diffusion. Figure 2 shows the breakpoints used to interpret the results.
- Where multiple isolates were collected from the same group of animals within a farm, one isolate was randomly selected and included in further analysis.
- Only antimicrobials for which more than 25 isolates were tested were included in the analysis.
- After these steps, 929 isolates derived from swine samples and 4,083 isolates derived from cattle samples were retained in the dataset.
- The WHO classification scheme was used to identify antibiotic classes, including critically important antibiotic classes (CIAs) and highest priority critically important antibiotic classes (HPCIAs).
- MDR was defined as resistance to three or more antibiotic classes.
- Descriptive analysis was performed to investigate patterns in resistance to CIAs and HPCIAs, at the individual antibiotic level and at the class level, as well as MDR.
- Cuzick's tests for linear trends were carried out.
- Microsoft Excel was used to collate the data and Stata 15 was used to clean and analyse the data.



Results

Figure 1: Percentages of *Salmonella* isolates originated from samples received by the clinical scanning surveillance system harbouring MDR or resistance to at least one antibiotic within a CIA class, by year



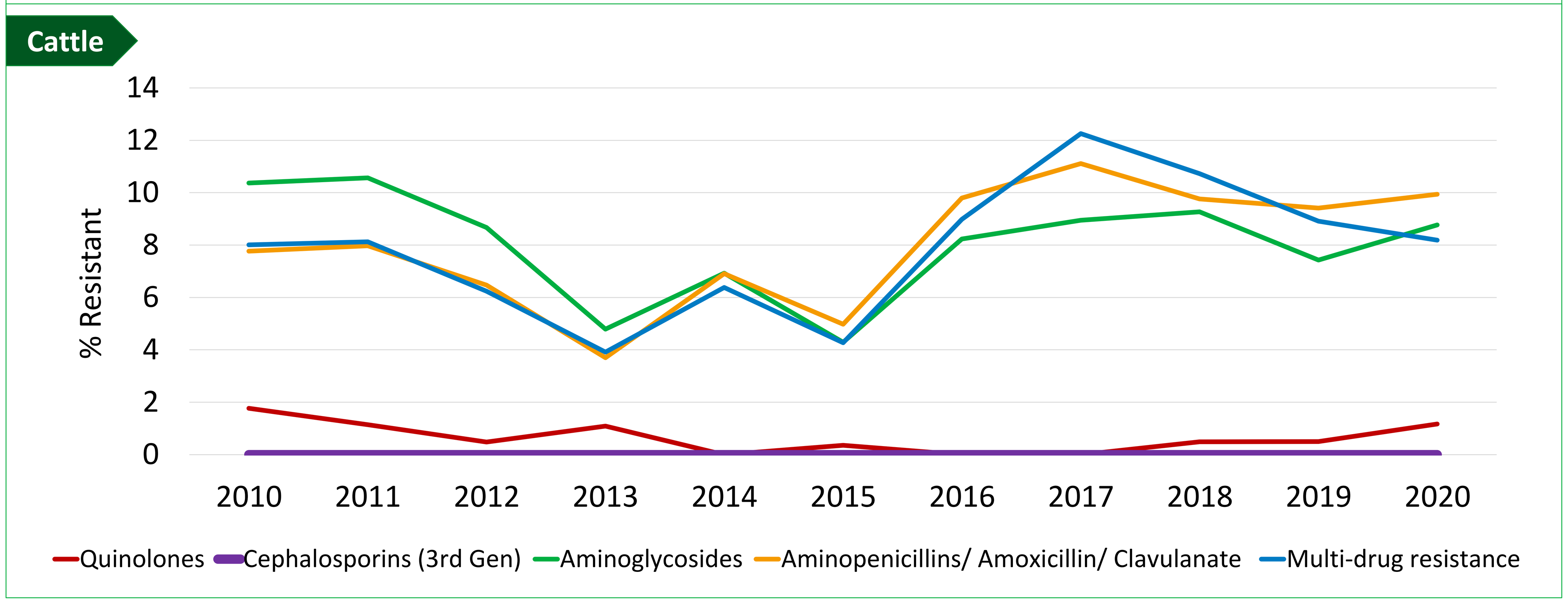


Figure 2: Percentages of isolates harbouring MDR, resistance to a CIA or resistance to at least one antibiotic within a CIA class; P-values from Cuzick's test for linear trend; and breakpoints used in susceptibility testing

Critically important antibiotics grouped into antibiotic classes	Breakpoint used*	Total proportion of isolates resistant across all years (%) / P-value from Cuzick's test for linear trend/ Direction of trend					
		Pigs			Cattle		
Quinolones - HPCIA		**2.1**	**<0.001**	↓	**0.8**	**0.005**	↓
Nalidixic acid	APHA	2.4	<0.001	↓	1.0	0.092	↓
Ciprofloxacin	BSAC	0.6	0.041	↓	0.2	0.043	↓
Enrofloxacin	BSAC	0.4	0.58	↑	0.1	0.236	↑
Cephalosporins (3rd Gen) – HPCIA		**0.3**	**0.429**	↓	**0.0**	**-**	
Ceftazidime	BSAC	0.4	0.705	↓	0.0	-	
Cefotaxime	BSAC	0.4	0.745	↓	0.0	-	
Cefpodoxime	BSAC	0.0	-		0.0	-	
Aminoglycosides – CIA		**75.6**	**<0.001**	↓	**8.4**	**0.064**	↓
Amikacin	BSAC	0.0	-		0.0	-	
Streptomycin	BSAC	80.7	0.599	↓	10.1	0.031	↑
Gentamicin	BSAC	14.5	0.685	↓	0.2	0.053	↑
Apramycin	APHA	17.8	0.26	↓	0.2	0.394	↑
Neomycin	APHA	11.3	0.115	↑	0.7	0.838	↑
Aminopenicillins/ Amoxicillin/ Clavulanate - CIA		**80.0**	**0.568**	↑	**7.6**	**0.045**	↑
Ampicillin	BSAC	80.0	0.583	↑	7.6	0.042	↑
Amoxicillin clavulanate	BSAC	1.1	0.021	↑	0.5	<0.001	↑
Multi-drug resistance		**82.9**	**0.001**	↓	**7.5**	**0.115**	↑

*BSAC refers to British Society for Antimicrobial Chemotherapy human breakpoints; APHA breakpoints are as described in the UK- VARSS Report.

Conclusions

Pigs:

- Figure 2 shows that there was evidence of a downward trend in the proportion of isolates resistant to quinolones (p<0.001). This was due to downward trends in resistance to two of the antibiotics in the class; nalidixic acid (p<0.001) and ciprofloxacin (p=0.041).
- For cephalosporins (3rd gen), levels of resistance were under 2% in all years (Figure 1), with no resistant isolates detected from 2016 onwards. There was no evidence of a trend at the class level or for any of the antibiotics in the class.
- From 2015 to 2019, the proportion of isolates resistant to aminoglycosides decreased from 88.9% to 46.8% (Figure 1). There was evidence of a downward trend (p<0.001) at the class level from 2010 to 2020 (Figure 2), despite no evidence of a trend for any of the antibiotics in the class.
- There was no evidence of a trend in resistance at the class level for aminopenicillins/ amoxicillin/ clavulanate, or for the ampicillin antibiotic. Levels of resistance to amoxicillin clavulanate were very low, but there was some evidence of an increasing trend (p=0.021, Figure 2).
- In total, 82.9% of isolates tested were found to be MDR across all years (Figure 2). However, Figure 1 shows that, from 2014 to 2018, the proportion decreased from 91.9% to 72.6% and there was evidence of a downward trend (p=0.001, Figure 2) over the studied period of time.

Cattle:

- Figure 2 shows that there was evidence of a decreasing trend in the proportion of isolates resistant to quinolones (p=0.005). However, as shown by Figure 1, this appears to mainly relate to earlier years, with the proportion increasing each year from 0.0% in 2017 to 1.2% in 2020. Very low levels of resistance to ciprofloxacin were detected in 2010 and 2011 with no resistant isolates detected from 2012 onwards (p=0.043, Figure 2). In contrast to the results for pigs, there was no evidence of a downward trend in resistance to nalidixic acid.
- No isolates tested were found to harbour resistance to cephalosporins (3rd gen) in any year (Figure 1).
- There was no evidence of a linear trend in resistance to aminoglycosides at the class level. However, there was some evidence of an increasing trend in resistance to streptomycin (p=0.031, Figure 2). For gentamicin, a p-value of 0.053 was obtained for an increasing trend (Figure 2). This differs to the results for pigs which indicated a decreasing trend at the class level but no evidence of trends for any of the antibiotics in the class.
- There was some evidence of an increasing trend in resistance to aminopenicillins/ amoxicillin/ clavulanate at the class level (p=0.045, Figure 2) and to ampicillin (p=0.042, Figure 2), whereas the results for pigs showed no evidence of a trend in either case. Rates of resistance to amoxicillin clavulanate were very low, but there was evidence of an increasing trend (p<0.001, Figure 2).
- Across all years, 7.5% of isolates tested were found to be MDR (Figure 2). In contrast to the results for pigs, there was no evidence of a linear trend in the proportion of MDR isolates.

Overall this study has helped to highlight the CIA classes and individual antibiotics associated with the highest levels of AMR, and those showing increasing and decreasing trends over time. These results can help guide the direction of further research, including risk factor analysis, to help inform control strategies targeting the biggest threats.

Next Steps

The results presented here do not take into account the effects of other factors, e.g. production type or age. Further analysis will therefore be performed, including the use of multivariable logistic regression, to identify associations between AMR and potential risk factors using routinely collected data: year of submission, age category, sample type, organic production, farm type, outdoor access, presenting sign, serogroup, and geographical region of farm.

Acknowledgements

- We wish to thank all of the farmers, veterinarians and private laboratories who submitted samples as part of the clinical scanning surveillance.
- The work carried out here was funded by the Veterinary Medicines Directorate (VMD), UK, under project code VM0533C.

Veterinary Medicines Directorate

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