Reduction of antibiotic use and antibiotic resistance in commercial poultry

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Introduction

Use of antibiotics for companion animals and livestock in the Netherlands has reduced by more than 60% over the last 10 years (SDa 2019; MARAN-2019). This reduction is the result of a change in policy towards the use of antibiotics in veterinary practice and is characterized by a series of coherent political decisions which changed the playing field for farmers and veterinarians considerably. In the years before 2009 the Netherlands was a high consumer of antibiotics in veterinary practice (Grave et al., 2010). The ban of antimicrobial growth promoters (AGPs) did not result in a reduction in total use since in the Netherlands the AGPs were fully replaced by antibiotics licensed for therapy. The total sales of all antibiotics remained stable at around 600 tons from 2000 to 2009.

This use pattern resulted in high levels of antimicrobial resistance in bacteria from livestock and food thereof and high prevalence of Livestock Associated MRSA and ESBL-producing *E. coli* and *Salmonella* (MARAN, 2019; RIVM, 2009). Specifically, ESBL-producing isolates in the food chain were considered a risk for public health and their high prevalences, predominantly but not solely in poultry and poultry meat products were the direct reason to initiate the change in policy towards antibiotic use in animals.

In this manuscript the trends in antibiotic use in poultry will be explored in the context of total use in livestock and its effect on the occurrence and trends in ESBL-producers and antimicrobial resistance in other bacterial species from poultry.

Trends in antibiotic use

Antibiotic use in the broiler, dairy and pig sector was monitored by LEI Wageningen UR during the 2004-2012 period, based on a stratified sample of farms. As of 2011 and 2013 the Netherlands Veterinary Medicines Institute (SDa) has full coverage usage data for the broiler and turkey sector, respectively. The data from these two sources have been combined to be able to describe long term trends in use. Because the LEI data is based on a sample, confidence intervals are wider in comparison with more recent data, when full coverage was realized. National antibiotic usage is measured as the number of daily dosages per animal year (first expressed as DD/AY, since 2012 as $DDDA_{NAT}$). This is calculated by dividing the number of kilograms of animal that could be treated with each active ingredient (treatable weight) by the total kilograms of animal present within a livestock sector (SDa, 2019).

An increase in antibiotic use was seen in the broiler sector until 2008, and a steep decline in the 2009-2018 period. This decrease was initiated after the government set three targets for reduction in antibiotic use: -20% in 2011, -50% in 2013 and -70% in 2015 compared to reference year 2009). The broiler sector has managed to achieve a 68% reduction in 2018, compared to 2009 (figure 1). The turkey sector was first monitored in 2013, after an initial rise use started to decline in 2016. Use continued to decline substantially in 2018 and over the 2013-2018 period its antibiotic use has dropped by 40.6% (SDa, 2019).

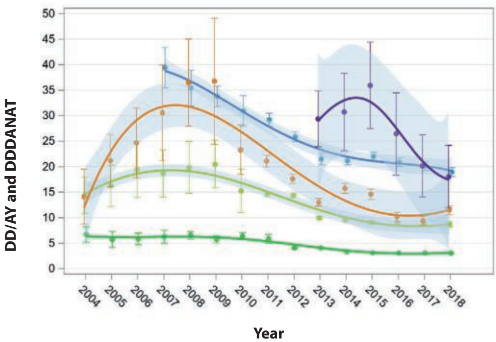

Figure 1. Long-term developments in antibiotic use according to LEI Wageningen UR data (in DD/AY, as published in MARAN reports, until 2010) and Veterinary Medicines Institute data (in DDDANAT, from 2011 onwards), as splines with point estimates and corresponding 95% confidence intervals for each year (adapted from SDa, 2019). Orange: broilers, purple: turkey, blue: veal calves, light green: pigs, green: dairy cattle.

Overall sales of antibiotics licensed for therapeutic use in animals declined by 63.8% between 2009 and 2018 (SDa, 2019). Critical success factors for this decrease were the governmental targets, measures taken by private quality systems in the livestock sectors and the SDa, which defined benchmark values for antibiotic use at farm level in the monitored livestock sectors in 2013. Antibiotics used in veterinary medicine were divided into first-, second- and third-choice antibiotics according to their importance for human health care. For the broiler sector the proportion of second choice broad-spectrum antibiotics usage of total usage has increased from 66% to 77% during the past five years, which is somewhat concerning.

Figure 2 A and B show distributions of antibiotic usage at farm level (expressed in $DDDA_F$) for the broiler sector, for 2013 and 2018. The number of farms with zero usage has increased considerably during this period. Turkey farms with zero usage have also increased, and the distribution became less right-skewed during this period. In 2013 turkey farms frequently reported high usage (more than 50 $DDDA_F$), in 2018 the number of farms showing high usage has decreased considerably.

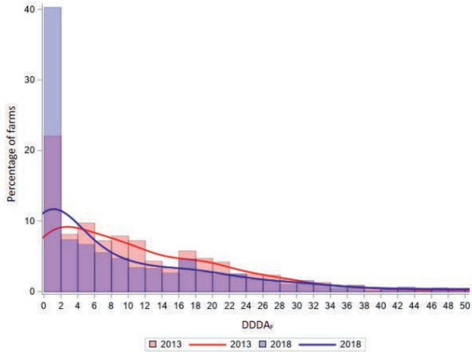

Figure 2A: 2013 and 2018 $DDDA_F$ distributions for broiler farms.

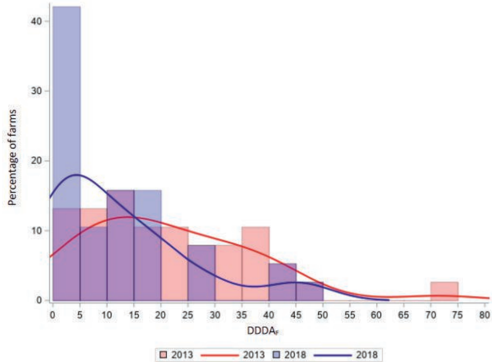

Figure 2B: 2013 and 2018 $DDDA_F$ distributions for turkey farms.

Trends in antibiotic resistance

European Food Safety Authority (EFSA) prescribes the sampling strategy and isolation methodology of bacteria from caeca of randomly picked food-producing animals at slaughter with the aim to detect the occurrence and trends in resistance at the bacterial population level in food animals. In the Netherlands, this monitoring is conducted in slaughter pigs and broilers since 1998. From 2005 onwards, resistance in isolates from both dairy cattle, veal calves and meat samples have been included.

EU legislation on monitoring and reporting of antimicrobial resistance (AMR) in zoonotic and commensal bacteria (2013/652/EU) was implemented in 2014. This includes susceptibility testing by broth microdilution according to ISO 20776-1:2006 with mandatory panels of antimicrobials. Results are interpreted with epidemiological cut-off values (ECOFF's) according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST). In this report non-wild type susceptible isolates are classified as resistant. These isolates all harbour an acquired resistance mechanism but may for some antibiotics not be clinically resistant.

Based on the results of the ongoing Dutch AMR monitoring program in livestock, information is presented on resistance in *E. coli*, as indicator organism for the occurrence and trends in resistance in Gram-negative bacteria in the gastro-intestinal tract of food-producing animals in the Netherlands. In addition, information is also provided about prevalence of ESBL-producing *E. coli* in the intestinal tract of broilers and meat in the last five years.

Indicator E. coli

Figure 3 shows the trends in proportions of resistance (%) of randomly *E. coli* isolated from faecal samples of broilers in the Netherlands from 1998 – 2018. High proportions of resistance were observed during the whole period of monitoring for ampicillin, sulfamethoxazole, trimethoprim, tetracycline and ciprofloxacin. For cefotaxime, chloramphenicol, colistin and gentamicin the proportions of resistance were lower in the same period. Still, the figure clearly shows a period of increasing resistances from 1998 – 2010 followed by a decrease from 2011 – 2017 for most antibiotics (Hesp et al., 2019). In the last years, proportions of resistance stabilized. In meat, similar trends in resistance were observed over time (MARAN,2019).

Cefotaxime resistant indicator E. coli

Since 1998, cefotaxime resistance of indicator *E. coli* was observed at low levels in all animal species. Figure 4 shows the percentage of cefotaxime resistant ESBL/AmpC-producing *E. coli* randomly picked from non-selective media derived from broilers, slaughter pigs (1998 – 2017), veal calves and dairy cows (2005 – 2017). In broilers, after 2003 an apparent increase in cefotaxime resistance was observed up to levels that varied between 15 – 20%, with the highest peak observed in 2007. The strong decline observed in 2011, from 18.3% to 8.1%, was most likely due to the decreased usage of antibiotics as reported above. Moreover, since the spring of 2010 the (off label) use of ceftiofur at Dutch hatcheries was ceased. A continuous low proportion of ESBL/AmpC-producing *E. coli* in broilers was observed in the last five years (<3%) and this was confirmed by the low level of cefotaxime resistance in 2017 (1.7%).

Selective isolation of ESBL/AmpC-producing E. coli

In parallel with the random non-selective isolation of ESBL/AmpC-producing *E. coli*, selective isolation was performed from caecal samples of livestock, which provides information on the prevalence of ESBL/AmpC-producing isolates (proportion of animal carriers). For broilers, a decreasing trend was observed over time, with a prevalence that started in 2014 at 66.0%, which gradually reduced in 2018 to 23.0% (figure 5).

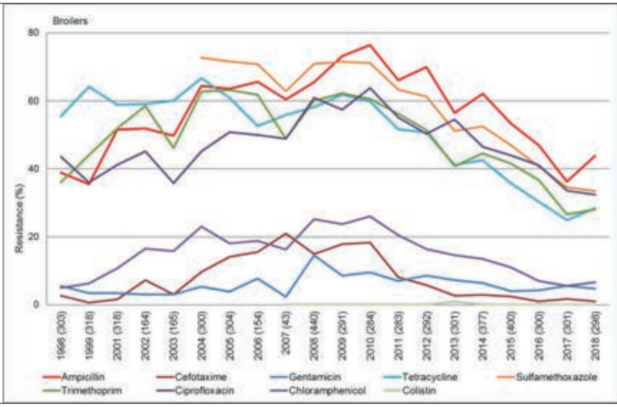

Figure 3. Trends in proportion of resistance (%) of *E. coli* isolated from faecal samples of broilers in the Netherlands from 1998 – 2018 (MARAN-2019).

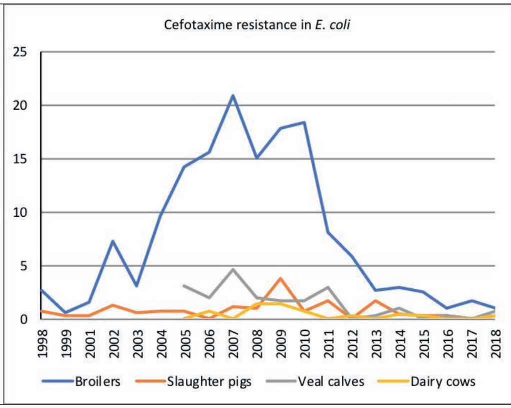

Figure 4. Trends in cefotaxime resistance (%) of *E. coli* randomly isolated from faeces of broilers, slaughter pigs, veal calves and dairy cows.

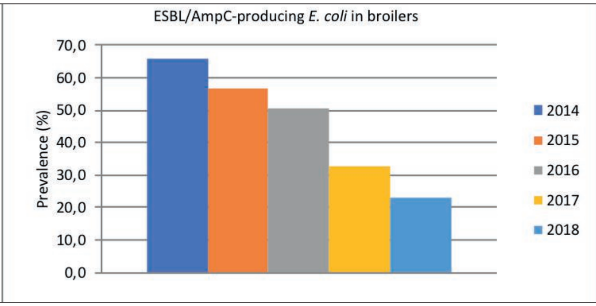

Figure 5. Trends in prevalence of animal carriers of ESBL/AmpC-producing *E. coli* in broilers from 2014 – 2018.

Conclusions and recommendations

It can be concluded that the measures initiated in the Netherlands were highly effective to reduce overall antibiotic use and more specifically antibiotic use in broilers. These measures resulted in a dramatic decrease in ESBL/AmpC-producing isolates in this livestock species. Success factors were the overall reduction in use, but specifically the abrupt ending of the highly unwanted off-label use of a third-generation cephalosporin in day-old chickens, which selected for ESBL/AmpC occurrence and spread in the poultry production chain.

References

Grave K, Torren-Edo J, Mackay D., Comparison of the sales of veterinary antibacterial agents between 10 European countries., J Antimicrob Chemother. 2010 Sep;65(9):2037-40.

MARAN 2019: Monitoring of Antimicrobial Resistance and Antibiotic Usage in Animals in the Netherlands in 2018.

Veegerelateerde MRSA: epidemiologie in dierlijke productieketens, transmissie naar de mens en karakterisatie van de kloon. RIVM-rapport 330224001, 2009.

The Netherlands Veterinary Medicines Institute (SDa), 2019. Usage of Antibiotics in Agricultural Livestock in the Netherlands in 2018. SDa/1153/2019.

Hesp A, Veldman K, van der Goot J, Mevius D, van Schaik G., Monitoring antimicrobial resistance trends in commensal Escherichia coli from livestock, the Netherlands, 1998 to 2016, Euro Surveill. 2019 Jun;24(25).