

Unintended consequences associated with national-level restrictions on antimicrobial use in food-producing animals



Among actions needed to address the antimicrobial resistance crisis are restrictions on the use of medically important antimicrobials in food-producing animals, which are often administered through national-level policy. One example is the complete restriction of antimicrobials for growth promotion, as recommended in WHO guidelines on use of medically important antimicrobials in food-producing animals.¹ The obvious intended consequence is reduced antimicrobial resistance but there could also be unintended consequences, such as harm to animal health and added cost of production. Some people in the agriculture sector fear serious consequences which deters implementation of the needed restrictions. We reviewed the published evidence on unintended consequences associated with national-level restrictions. We used keyword searches in Ovid MEDLINE and AGRICOLA databases to identify interventional or observational studies that reported national-level restriction of antimicrobial use in food animals, and compared non-antimicrobial resistance outcomes between intervention and comparator groups in food animals or in humans. Eligible antimicrobial use restrictions included mandatory or voluntary prohibition of antimicrobial use, limitations on specific drug classes, and incentives for reduced antimicrobial use. The search identified 14 articles, all from Europe (table).

Several studies focused on bans on antimicrobial growth promoters (AGPs). AGP bans in Sweden and Denmark (but not Finland) were initially accompanied by increased diarrhoea in weanling pigs, but little or no increased disease in other species.^{11,14,15} In Denmark, bans resulted in temporary increases in therapeutic use of some medically important antimicrobials leading to antimicrobial resistance problems in *Salmonella* spp from pigs and humans.¹⁴ In both countries, these problems were addressed by improvements in animal health management and housing.^{14,15} In Norway, the ban resulted in increased use of amoxicillin for treatment of necrotic enteritis in broilers, but overall a 39% decrease in antimicrobial use for treatment or disease prevention was reported.^{9,10} In the Netherlands, the AGP ban was initially accompanied by a compensatory increase in antimicrobial use for treatment or disease prevention;

however, in Switzerland the ban did not result in increased use of feed antimicrobials for treatment or disease prevention in swine.^{5,13} The experiences of European countries that terminated AGPs suggest that other countries considering similar action should implement measures to minimise disease in vulnerable animals, especially weanling pigs. Care is needed to avoid compensatory increases in antimicrobial use for treatment or disease prevention by improving veterinary oversight, linking antimicrobial use surveillance to remedial action on excessive use, mandatory antimicrobial use reduction targets, and improvements in animal health.

AGPs are ostensibly used to improve the efficiency of production. For 2 years after AGP termination in Denmark there were some production losses in weanling pigs, but over the long term, AGP termination had little discernible effect on production.^{2,14} In broilers, production losses were offset by savings in AGP costs.⁸ Estimates of AGP effects (eg, average daily gain and feed conversion ratio) vary widely, ranging from 0% to 15% and have declined to 0–5% since the early 2000s.¹⁶ AGPs are believed to be most beneficial when animals are raised in overcrowded and unhygienic conditions. Substantial improvements in housing, nutrition, health management, and animal genetics could explain declining efficacy of AGPs.¹⁶

Economic effects of AGP termination in Denmark were evaluated by estimating costs of animal production, economic efficiency of broiler production, and effects on the Danish economy; the estimated effects were small (table).^{12,14} Other potential adverse consequences that were assessed included effects on food safety (none identified) and environmental effects (some concerns from increased use of oral zinc oxide for prevention of pig diarrhoea).^{14,15}

Unintended consequences from antimicrobial use restrictions for disease treatment or prevention have also been assessed. In 2010, Denmark introduced the Yellow Card system of restrictions on pig farmers that used twice the average quantity of antimicrobials resulting in a substantial reduction in antimicrobial use in Danish pigs with no adverse effects on mortality and production.^{3,7} The programme's influence on the occurrence of lesions

	Country	Study design	Type of restriction	Unintended consequences evaluated	Adverse consequences of restriction*
Aarestrup et al (2010) ²	Denmark	Longitudinal (before and after), 1993–2008	AGP termination, 1999	Mortality in piglets and weanling pigs, mean number of pigs produced per sow per year, average daily gain in weanling and finishing pigs, percentage of dead or condemned finishing pigs, feed unit per kg of gain in finishing pigs	Small, 1–2 year increase in mortality (approximately 0.6%) and drop in average daily gain (approximately 2.6%) in weanling pigs
Aarestrup (2015) ³	Denmark	Longitudinal (before and after), 1994–2013	Yellow Card system of imposed measures in pig herds with highest antimicrobial consumption per pig	Mortality in piglets and weanling pigs; mean number of pigs produced per sow per year; average daily gain in weanling and finishing pigs, percentage of dead or condemned finishing pigs	No adverse consequences identified
Alban et al (2013) ⁴	Denmark	Longitudinal (before and after), 2010–11	Yellow Card system.	Prevalence of nine lesions in finishing pig carcasses at slaughter	Increase in chronic peritonitis (OR 1.5), umbilical hernia (OR 1.2), and chronic enteritis (OR 1.2) but decrease in tail bite infection (OR 0.6), chronic pericarditis (OR 0.6), and chronic pneumonia (OR 0.7)
Arnold et al (2004) ⁵	Switzerland	Longitudinal (before and after), 1996–2001	AGP termination, 1999	Use of antimicrobials in feed for treatment and disease prevention of piglets and fattening pigs	No adverse consequences identified
de Jong et al (2013) ⁶	Netherlands	Longitudinal, risk factor analysis, 2011–12	Mandatory antimicrobial use reduction targets	Incidence of mortality and hock burn in broilers	No adverse consequences identified
Dupont (2016) ⁷	Denmark	Longitudinal (before and after), 2010–11	Yellow Card system	Animal health, mortality and daily weight gain, changes in lean meat percentage, and prevalence of lesions at slaughter	Increase in mortality (0.7%) in weanling pigs, increased localised tail bites (OR 1.8), chronic peritonitis (OR 1.3), and abscesses in heads and ears (OR 1.2) but decreased pleuritis (OR 0.9), abscesses in feet and legs (OR 0.7), abscesses in front, mid, and rear sections (0.84), chronic pneumonia (OR 0.8), and infected tail bites (OR 0.4)
Emborg et al (2001) ⁸	Denmark	Longitudinal (before and after), 1995–99	AGP termination, 1998	Broilers produced (kg per square metre), feed conversion ratio, total percent dead broilers	Increased feed conversion ratio (0.016 kg/kg increase) until end of study
Grave et al (2004) ⁹	Norway	Longitudinal (before and after), various years	AGP termination (avoparcin), 1995	National consumption of antimicrobials for treatment and disease prevention in broilers; percentage of broiler chicken flocks treated for necrotic enteritis	Increase in use of amoxicillin (by approximately 50 kg per annum nationally), but decrease in use of penicillin (by approximately 25 kg per annum) to negligible levels; increase in percentage of broiler chicken flocks treated for necrotic enteritis of 10.1% in first year only following termination
Grave et al (2006) ¹⁰	Norway	Longitudinal (before and after), 1993–2003	AGP termination, 1995	National consumption of antimicrobials for treatment and disease prevention (poultry and pigs)	No adverse consequences identified
Laine et al (2004) ¹¹	Finland	Longitudinal (before and after), 1999–2000	AGP termination, 1999	Use of antimicrobials for treatment and disease prevention; incidence of diarrhoea; piglets weaned per sow per year, percent mortality, age at weaning (days)	Increase in treatment for diarrhoea in 14% of herds
Lawson et al (2008) ¹²	Denmark	Longitudinal (before and after), 1994–2004	AGP termination, 1998	Effect on economic efficiency of broiler production	No adverse consequences identified
Mevius et al (2011) ¹³	Netherlands	Longitudinal (before and after), 1999–2009	AGP termination over period 1999–2006	National consumption of antimicrobials for treatment and disease prevention	National consumption of antimicrobials for treatment and disease prevention (grams/kg live weight [all species]) increased by 85% 1999–2007 then decreased 15% by 2009

(Table continues on next page)

in slaughter pigs was mixed (table).⁴ In 2009, the Dutch poultry industry voluntarily discontinued use of fluoroquinolones and third generation cephalosporins, and in 2013, the swine industry voluntarily discontinued use of third generation cephalosporins. No adverse effects were reported.¹⁷ In 2010, the Dutch government set mandatory targets for reduction of antimicrobial use for treatment or disease prevention in food animals of 20% by 2011, 50% by 2013, and 70% by 2015. Additional restrictions included no use of new antimicrobials (eg, carbapenems) in animals, only permitting the use of

fluoroquinolones and cephalosporins with evidence that other antimicrobials would be ineffective, and making colistin, β-lactams, and aminoglycosides second-choice antimicrobials.¹⁸ Non-quantitative reports of resulting disease problems in pigs have been published but there has not been sufficient time to fully assess effects of the reduction programme.¹⁷ No effects on mortality and morbidity in broilers were identified.⁶

The lack of relevant studies from outside Europe raises questions about the global generalisability of the findings of this review, particularly for low-income

	Country	Study design	Type of restriction	Unintended consequences evaluated	Adverse consequences of restriction*
WHO (2003) ¹⁴	Denmark	Longitudinal (before and after), 1999–2002	AGP termination over period 1995–99	National consumption of antimicrobials for treatment and disease prevention; prevalence of antimicrobial resistance in foodborne bacteria in animals, food, and humans; effects on food safety (incidence of antimicrobial residues in food or incidence of human <i>Salmonella</i> , <i>Campylobacter</i> , or <i>Yersinia</i> infections); effects on animal health and welfare; effects on environment (heavy metals, soil nutrients, bacteria, and antimicrobial residues); effects on animal production (total production, mortality, average daily gain, feed efficiency; cost of pig and poultry production, effects on national economy	Average increase of 46.5% (mainly in weanling pigs) in use of antimicrobials for treatment and disease prevention in 2 years following termination of AGPs in 1999 (increased use of aminoglycosides, macrolides, penicillins, tetracyclines, and sulphonamide or trimethoprim); increased tetracycline resistance (approximately 10%) in <i>Salmonella</i> from human infections; increased rate of antimicrobial treatment for diarrhoea in pigs by approximately 0.6 treatments per pig month at risk in weanling and grower or finishing pigs, increased necrotic enteritis diagnoses in broilers from 1–2 per 1700 flocks in the year before termination to 25 per 1700 in the year after termination; increase of 1.6 days to reach 100 kg bodyweight, 0.6% increase in mortality in weanling pigs, decrease of 2.6% in average growth rate of weanling pigs. decreased feed efficiency in poultry (-2.3%); increased cost of approximately 7.75 DKK per pig produced resulting in an increase in pig production costs of approximately 1%. Overall negative effect of termination on economy of 0.03% (363 million DKK) by 2010 (at 1995 prices) in real gross domestic product.
Wierup (2001) ¹⁵	Sweden	Longitudinal (before and after), 1980–99	AGP termination, 1986	National consumption of antimicrobials for treatment and disease prevention; preweaning and postweaning mortality, age at 25 kg and 30kg, mean number of pigs produced per sow per year	Compared with 1986 (24 903 kg active antimicrobials), total use of antimicrobials for treatment and disease prevention increased 21.2% in 1988, remained stable to 1994, and reduced by at least 17% (of 1986 amounts) between 1996 and 1999. In the first year after termination weanling pig mortality increased by approximately 1.5%, age at 25 kg increased by 5–6 days and age at 30 kg increased by 2 days.

AGP=antimicrobial growth promoter. OR=odds ratio. *Data from some countries appear in multiple studies (eg, related to AGP termination in Denmark); findings of adverse effects are listed only for the first published study, unless additional information was provided in subsequent studies.

Table: Characteristics and findings of studies that reported on unintended consequences from national-level restrictions on use of antimicrobials in food-producing animals

countries. Clearly, more data from other parts of the world would be useful. Research investigating the effects of antimicrobial resistance interventions in agriculture and aquaculture, such as a study¹⁹ underway in Vietnam, should be encouraged to document unintended consequences. Moreover, as global surveillance of antimicrobial resistance and antimicrobial use improves and more countries implement national-level antimicrobial stewardship initiatives in food animals, it is important to further evaluate and report unintended consequences.

Overall, the available evidence indicates that unintended consequences from national-level restrictions on antimicrobial use in food animals were temporary and minor. Despite the Eurocentric nature of the data, the global implementation of appropriate restrictions at national level should not be delayed, such as those recommended in the WHO guidelines.¹ Some problems can be expected, particularly in intensive livestock farming (eg, diarrhoea in weanling pigs following AGP ban), but these effects could be mitigated by improvements to animal health management and housing. Making these improvements can be challenging, especially in low-income countries, and might require support from other countries, the UN Food and Agriculture Organization, and the World Organisation for Animal Health. Despite the data gaps, the experience from Europe

indicates that restrictions on antimicrobial use in food animals, such as those recommended by WHO, can be implemented without serious harm.

Scott A McEwen, Frederick J Angulo, Peter J Collignon, John M Conly

Department of Population Medicine, University of Guelph, Guelph, ON N1G 2W1, Canada (SAM); Division of Global Health Protection, Center for Global Health, Centers for Disease Control and Prevention, Atlanta, GA, USA (FJA); Infectious Diseases and Microbiology, Canberra Hospital, Canberra, ACT, Australia (PJC); Medical School, Australian National University, Acton, ACT, Australia (PJC); and Departments of Medicine, Microbiology, Immunology & Infectious Diseases, and Pathology & Laboratory Medicine, Synder Institute for Chronic Diseases and O'Brien Institute for Public Health, Cumming School of Medicine, University of Calgary and Alberta Health Services, Calgary, AB Canada (JMC)

smcewen@uoguelph.ca

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