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A cross-sectional study of oral antibacterial treatment patterns in relation to specific diarrhoeal pathogens in weaner pigs

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ABSTRACT

According to international guidelines, the use of antibacterials should be evidence based and prudent. This register-based, cross-sectional study investigates the potential effect of laboratory findings on the patterns of antibacterial oral (batch) medication of weaner pigs, and the level of compliance with national guidelines for antibacterial use. The study population includes 1,736 weaner herds (≈65% of all Danish weaner pigs) that were subject to laboratory analysis from the National Veterinary Institute on *Brachyspira pilosicoli, Lawsonia intracellularis,* and *E.coli* (F4 and F18) in 2014. Antibacterial prescription data were obtained from the national database, VetStat. These showed that antibacterial prescriptions for use in weaner pigs was 8.6% lower in spring 2015 compared to spring 2014. The antibacterial use per pig tended ($p = 0.08$) to decrease more in herds with negative laboratory results compared to herds with a moderate or massive occurrence of either of the pathogens. Irrespective of the laboratory findings on diarrhoeal pathogens, tetracyclines were the most frequently used antibacterials by a substantial margin, both 3 months prior to and 2-5 months after laboratory analysis. According to the national guidelines, tetracyclines are the second or third-choice antibacterial for treatment of diarrhoeal pathogens, due to resistance and co-resistance patterns. Compliance with the guidelines increased in 14% of the herds, mostly following identification of *B. pilosicoli* within the herd. Between 10% and 20% of the herds did not use batch treatment, despite the presence of moderate–massive amounts of the pathogens.

1. Introduction

Strategies to combat the emergence of antibacterial resistance must be targeted at supporting non-antibacterial disease prevention and decreasing non-responsible use both in humans and animals (WHO, 2015). Numerous strategies have been applied to promote the prudent use of antibacterials (ranging from legal restrictions and treatment guidelines to information campaigns), and guidelines for antibacterial use in veterinary practice have been published internationally as well as in individual European countries (Teale and Moulin, 2012). A key step towards prudent antibacterial use is to decide whether the treatment is necessary, or if non-antibacterial prophylactic means should be implemented. In addition, the most appropriate antibacterial should be used. However, the decision to treat and choice of antibacterials may be affected by numerous factors other than professional veterinary knowledge (Busani et al., 2004; Vandeweerd et al., 2012; Gibbons et al., 2013; De Briyne et al., 2013; Coyne et al., 2014).

In Denmark, a number of legal interventions have been implemented in order to promote the prudent use of antibacterials (DANMAP, 2010). The vast majority of antibacterials used in the veterinary field are prescribed for pigs and as a consequence, a legal intervention called “The Yellow Card Initiative” was enforced in 2011, which imposes restrictions and preventive measures in the herds with the highest consumption per pig (Anonymous, 2011, 2014b). Antibacterials are usually administered to pigs (in particular weaners) per pen or section via feed or water, implying that healthy animals within the pens are also treated (Merle et al., 2012; Callens et al., 2012). However, oral administration appears to be a crucial factor in the risk of antibacterial resistance development (Burow et al., 2014).

Batch treatment is often used for preventive purposes in pigs, but practice and legislation differ amongst the individual European countries (Callens et al., 2012). In Denmark, prophylactic use is illegal, and all antibacterial use is by prescription only, requiring a diagnosis based on veterinary examination of the animal or herd (Anonymous, 2014a). Once a herd diagnosis is established, and if

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potential recurrent disease is indicated, metaphylactic treatment administered by the farmer is allowed – legally defined as treatment "in a well-defined incubation phase" – but only if a Veterinary Health Advisory Contract (VAC) is in place (Anonymous, 2014a). However, the criteria for discontinuing repeated treatment of consecutive batches of pigs are not clear. A British focus group study documented that both farmers and veterinarians found it difficult to decide when to withdraw prophylactic treatments (Coyne et al., 2014). A recent Danish study (Pedersen et al., 2015) found that 84% of the farmers used some clinical inspection criteria to determine when to initiate treatment, while antibacterials were used systematically on a fixed day post-weaning in 16% of the herds, suggesting a prophylactic application. Furthermore, recurrent monthly herd-level prescription of the same antibacterial occurs in a large proportion of Danish weaner herds (DANMAP, 2008).

According to the WHO action plan on antibacterial resistance (Anonymous, 2015a), evidence-based prescribing and dispensing should be standard practice. Official Danish treatment guidelines for pigs relate to the selection of antibacterials for treatment of specific pathogens (DANMAP, 2010), presupposing the identification of a causal agent. However, a recent Danish study indicated only a slight agreement between the veterinarians' clinical aetiological diagnosis and the diagnosis from laboratory examinations for gastrointestinal (GI) bacterial pathogens (Pedersen et al., 2015). Furthermore, diarrhoea may have a non-infectious or viral aetiology (Pluske et al., 2002; Chase-Topping et al., 2007). On 1st June 2014, the Danish Food Authority implemented a new article in the Health Advisory Contracts Order (Anonymous, 2014c) targeting antibacterial group medication, defined as in-feed or water medication of pigs. Laboratory diagnostics became mandatory in relation to the oral treatment of respiratory or GI disease in herds with a Veterinary Health Advisory Contract (VAC), and the veterinarian must sample and submit material from untreated pigs prior to antibacterial group medication. Depending on the laboratory results, the veterinarian must evaluate (and if indicated, rectify) the treatment, and/or submit supplementary samples. Ultimately, if a causal bacterial pathogen is not clearly identified, alternative treatment strategies must be considered. The resulting laboratory data provide information on the presence of specific bacterial pathogens at herd level in a large proportion of Danish pig herds.

The objectives of the current investigation were to: 1) determine whether the mandatory laboratory testing may have affected antibacterial use; 2) describe and assess the use of antibacterials for oral treatment of diarrhoea in weaner pigs, as well as the potential association with the laboratory findings; 3) evaluate whether the laboratory results were associated with a change in treatment strategy and compliance with the national guidelines for antibacterial treatment.

2. Materials and methods

2.1. Laboratory data

According to the legal order (Anonymous, 2014c), a submission of diagnostic samples in relation to the symptoms of GI disease should contain at least faecal samples, gut section or cadavers. The faecal samples must be collected before treatment as either a "sock sample" or a pooled faecal sample. It is often not possible to clearly differentiate between infections with the most common pathogens: *Brachyspira pilosicoli* (*B. pilosicoli*), *Escherichia coli* (*E. coli*, fimbria type F4 and F18), or *Lawsonia intracellularis* (*L. intracellularis*) from clinical symptoms alone (Pedersen et al., 2015), and the legal order therefore recommends analysis for all four pathogens. If the sample is positive for *E.coli,* antibacterial sensitivity testing of *E.coli* isolates is recommended. Other bacterial pathogens such as *Salmonella spp*. or *Brachyspira hyodysenteriae* might be suspected, though these are unlikely; *B. hyodysenteriae* is extremely rare in Denmark due to the Danish SPF-system and Salmonella is rarely detected in relation to clinical disease in pigs (Anonymous, 2016b). In a recent study of 20 randomly selected herds with outbreaks of diarrhoea, the four previously mentioned bacterial species were the only bacterial pathogens found (Pedersen et al., 2014).

The National Veterinary Institute (NVI) analysed the vast majority of samples that were analysed for the four pathogens in 2014 (Anonymous, 2015b). The samples submitted to the NVI for bacterial GI pathogen analysis were almost entirely faecal samples – either pooled samples or sock samples. The standard analysis of faecal samples includes quantitative PCR (q-PCR) for *B. pilosicoli*, *E. coli* (fimbriae type F4 and F18) and *L. intracellularis*. Analyses for individual pathogens using other methods were not included in the present investigation due to their sporadic occurrence. The

Table 1
Classification of weaning pig herds based on laboratory testing for gastrointestinal pathogens.[a]

Diagnosis group	Definition	Number of herds[b]	
		H1	H2
Negative	All samples tested negative for the 4 pathogens	85	83
Low-grade occurrence	Positive (>10^3 copies/gram) for at least one pathogen, less than moderate occurrence of all pathogens	102	102
Moderate–massive occurrence			
ECOLI positive	>10^5 copies/gram faeces	1530	442
BPILO positive	>10^4 copies/gram faeces		46
LAWS positive	>10^5 copies/gram faeces		171
ECOLI and LAWS positive	LAWS > 10^5 and/or ECOLI > 10^5 copies/gram faeces Both pathogens > 10^3 copies/gram faeces		332
ECOLI and BPILO positive	BPILO > 10^4 and/or ECOLI > 10^5 copies/gram faeces Both pathogens > 10^3 copies/gram faeces		94
LAWS and BPILO positive	BPILO > 10^4 and/or LAWS > 10^5 copies/gram faeces Both pathogens > 10^3 copies/gram faeces		187
LAWS, BPILO and ECOLI positive	BPILO > 10^4 and/or LAWS > 10^5 and/or ECOLI> 10^5 copies/gram faeces Three pathogens >10^3 copies/gram faeces		196
Total		1717	1653

[a] Laboratory analysis for GI pathogens: ECOLI = *E. coli;* BPILO = *B. pilosicoli;* LAWS = *L. intracellularis*.
[b] Number of herds included for investigation of Hypothesis 1 (H1) and Hypothesis 2 (H2) respectively, after omission of outliers (for H1) and omission of herds with more than 3 months between submission and final laboratory result (H2).