Food Control 98 (2019) 126–132

Contents lists available at ScienceDirect

Food Control

journal homepage: www.elsevier.com/locate/foodcont

# Improving antimicrobial residue surveillance in finishing pigs by risk-based sampling designs

Anouk Veldhuis[a,*], Lis Alban[b], Derk Oorburg[c], Gerdien van Schaik[a,d]

[a] GD Animal Health, PO Box 9, 7400, AA Deventer, the Netherlands
[b] Danish Agriculture & Food Council, Department for Food Safety and Veterinary Issues, Axeltorv 3, DK-1609, Copenhagen V, Denmark
[c] Vion, PO Box 1, 5280, AA Boxtel, the Netherlands
[d] Utrecht University, Faculty of Veterinary Medicine, Department of Farm Animal Health, Utrecht, the Netherlands

ARTICLE INFO

*Keywords:*
Residue surveillance
Scenario tree modelling
Economic evaluation

ABSTRACT

EU Member States are obliged by legislation to implement residue surveillance programs to detect illegal use or misuse of veterinary medicines in food producing animals and investigate the reasons for residue violations. According to EU legislation, these programs should be (partly) risk-based, meaning targeted towards groups of animals, where the probability of finding residues is the highest. There is however no default surveillance procedure describing the most efficient way to do so. In this study, a quantitative analysis was conducted to quantify the effectiveness of detecting antimicrobial residues in finishing pigs via risk-based sampling of carcasses. A stochastic scenario tree analysis was applied to estimate the sensitivity of random and risk-based sampling strategies to detect a contaminated carcass. In these models, the probability was calculated that a single carcass will yield a positive outcome when subjected to the testing protocol laid down in the design, given that contamination with antimicrobial residues is prevalent in the herd of origin at the level of the design prevalence. Two design prevalences were used: 0.01% (the assumed true prevalence of residue-positive carcasses) and 0.22% (the prevalence that can be detected using the sample size laid down in EU legislation). In the random design, it was assumed that the carcasses examined for presence of antimicrobial residues were selected randomly from all finishing pigs slaughtered in a year. In the risk-based design, two risk factors were taken into account. First, a high prevalence of chronic pleuritis and pneumonia in the herd of origin was assessed. Secondly, the route of administration of antimicrobials (oral/parenteral) via visual inspection of skin lesions indicative of injectables was used as an additional risk factor. Results showed that the probability of detecting a residue-positive carcass doubled when surveillance was targeted at pigs originating from herds with a high prevalence of chronic pleuritis and pneumonia (compared to random sampling), at similar costs of testing. Including administration route as an additional risk factor led to a negligible increase in sensitivity. Nevertheless, sensitivity values at unit level remained extremely low due to the very low prevalence of antimicrobial residues in pigs. In this study, risk-based alternatives to random sampling improved the cost-effectiveness of residue surveillance in slaughter pigs in the Netherlands, which could be used to enhance current programs and to increase awareness in food business operators.

## 1. Introduction

Residues of veterinary medicinal products may be present in animal tissue and animal products, due toabsorption of pharmacologically active substances from the intestinal tract or due to injections into the body. For antimicrobials, the level of absorption from the intestinal tract depends on antibiotic-specific pharmacokinetics and the way the product is administered (e.g. orally, intravenously, or subcutaneously) (Katz, 1980; Mevius et al., 1989). Since the mid-1960s, it is believed that the presence of unauthorised substances or residues of veterinary medicinal products may pose a risk to public health. The availability of highly sensitive detection methods and the implementation of maximum residue limits (MRLs) by EU Member States has led to an increasing awareness of residues of potentially harmful substances in food and the demand for harmonization of MRLs through Community legislation (EC, 2003). The Community legislative framework on residues of pharmaceutically active substances or veterinary medicinal products in food was designed in the late 1980s and early 1990s. Most

* Corresponding author.
*E-mail address:* a.veldhuis@gdanimalhealth.com (A. Veldhuis).

https://doi.org/10.1016/j.foodcont.2018.11.022
Received 29 March 2018; Received in revised form 9 November 2018; Accepted 10 November 2018
Available online 12 November 2018
0956-7135/ 

importantly, Council Directive 96/23/EC, on measures to monitor certain substances and residues thereof in live animals and animal products, requires Member States to adopt and implement a national residue surveillance program for specific groups of residues. The Directive is typically input-based: it lays down sampling levels and frequency for bovines, pigs, sheep and goats, equines, poultry and aquaculture, as well as the groups of substances to be monitored for each food commodity (EFSA, 2016). According to the Directive, the objective of the surveillance program is to monitor and reveal the reasons for residue hazards in foods of animal origin. For residues of group B specifically (veterinary drugs and contaminants), surveillance should be aimed particularly at controlling the compliance with MRLs for residues of veterinary medicinal products (Anon., 1996). National residue surveillance programs should be (partly) risk-based, meaning targeted towards groups of animals, where the probability of finding residues is the highest (Anon., 1996). This form of surveillance generally leads to higher sensitivity and increased efficiency (cost-benefit) compared to surveillance conducted randomly across the population (Stärk et al., 2006). Ways to demonstrate cost-effective monitoring of antimicrobial residues is of relevance, because EU Directive 96/23/EC is currently being renegotiated (Alban, Léger, Veldhuis, & Van Schaik, 2018). The current study therefore aimed to quantify and compare the performance of random and risk-based sampling strategies to monitor antimicrobial residues in finishing pigs at slaughter in the Netherlands. For this purpose, stochastic scenario tree modelling and an economic evaluation were carried out.

## 2. Materials and methods

### 2.1. Antimicrobial residue surveillance in the Netherlands

The residue surveillance program in the Netherlands is characterized by an official national residue monitoring plan and a private program carried out by the largest abattoir company ('Vion'). A description of the two programs was made using the RISKSUR design tool. The tool, which was developed between 2012 and 2015 in a project funded by the Seventh Framework Program of the EU, guides in the development of animal health surveillance systems, with the aim of structuring the process of designing and documenting the surveillance program. The design tool is available online via the website http://www.fp7-risksur.eu. More details regarding the tool and its application to describing antimicrobial residue surveillance programs are described by Alban et al. (2018). For illustrative purposes, a completed version of the tool describing the official program is added as Supplementary material (Appendix A).

#### 2.1.1. Official program

Official monitoring of residues of antimicrobials in slaughter animals was initiated in the Netherlands in the late 1970s. According to EU legislation, Member States should sample 0.03% of all slaughtered pigs for monitoring of residues of group B, of which 30% of group B1 (antimicrobials). Yearly, about 15,000,000 pigs are slaughtered in the Netherlands, which means that 1350 of them should be sampled in the national residue surveillance plan to detect residues of antimicrobials to comply with EU legislation. Between 2012 and 2015, an average of 2451 samples (range: 2315–2622) were analysed yearly to detect presence of residues of antimicrobials in pig carcasses as part of the official program (NVWA, unpublished data). The diagnostic method used is a low-cost microbial screening assay, called the Nouws Antibiotic Test (NAT) (Pikkemaat, Oostra-van Dijk, Schouten, Rapallini, & van Egmond, 2008), followed by chemical confirmation of positive samples with high-performance liquid chromatography–mass spectrometry (HPLC LC-MS/MS). The microbial assay comprises a five-plate screening test (NAT-screening) based on the analysis of paper disks impregnated with renal pelvis fluid (pre-urine) (Pikkemaat et al., 2008) and two post-screening tests (NAT-postscreening) based on the analysis of meat fluid (Pikkemaat, Rapallini, Oostra-van Dijk, & Elferink, 2009a) and kidney fluid (Pikkemaat et al., 2009b). All test plates (screening and post-screening) are specific for one or two groups of antibiotics (tetracyclines, beta-lactam antibiotics/macrolides, quinolones, sulphonamides/diaminopyrimidines, or aminoglycosides). Post-screening is only performed for the residue type that is indicated by the screening. Subsequently, chemical confirmation and quantification of residue content of positive samples is carried out using a sample of meat. The sampling strategy in the official program is a combination of random and risk-based sampling, however due to the absence of a transparent, standardized sampling approach (in which selection criteria are well-described), the sampling strategy of the official program is considered random in this study.

#### 2.1.2. Private program

EU legislation prescribes that pig producers are not allowed to administer prohibited substances to animals nor to market animals for which prescribed withdrawal periods of administered veterinary medical products are not respected. In addition, processors (slaughterhouses) should take all necessary measures to ensure that only animals free of residues and prohibited substances are accepted for slaughter (Anon., 1996). The private program carried out by the abattoir is in place to fulfil these requirements. The private program has been in place since 2006. Between 2012 and 2015, an average of 6992 carcasses (range: 6098–7722 in a slaughter population of around 15,000,000) were analysed yearly to detect presence of residues of antimicrobials in finishing pig carcasses (Vion, unpublished data). The private sampling is risk-based such that only carcasses that originate from herds with a high within-herd prevalence of chronic pleuritis or pneumonia are sampled. This risk factor has been related to presence of residues of antimicrobials in pigs previously (Alban, Pacheco, & Petersen, 2014). A herd is considered a high-risk herd if in a batch of carcasses from this herd a prevalence of chronic pleuritis or pneumonia lesions is observed that is twice as high as the slaughterhouse meat inspection average. The slaughterhouse average is approximately 20% for chronic pleuritis and 5% for pneumonia, which is in agreement with other estimates from the Netherlands (Bondt et al., 2004) and Denmark (Alban et al., 2014). Once this threshold is violated, one carcass is selected randomly from the batch to be sampled for analysis, in which it is assumed that any randomly chosen pig will be representative for the batch of pigs. The classification of high-risk herds is based on the meat inspection results. The meat inspection is carried out by an inspector of the competent authority; the subsequent classification is an automated process. The diagnostic test protocol to detect residues of antimicrobials is identical to that of the official program.

### 2.2. Scenario-tree model

#### 2.2.1. Model structure

A scenario tree analysis was applied to the official program ('random design') and the private program ('risk-based design') to estimate the sensitivity of the surveillance system components to detect a contaminated carcass on a yearly basis. A stochastic scenario-tree model was developed for each surveillance design, as described by Martin, Cameron, and Greiner (2007a,b). In these models, the probability is calculated that a single unit (in this study: a carcass) will yield a positive outcome when subjected to the testing protocol laid down in the component. First, for each limb of the tree the conditional probabilities along the branch of the tree were multiplied together to give the overall probability of the limb's outcome. Then, the component sensitivity at unit level (CSeU) was calculated by summing the probabilities for all limbs with positive outcomes in the scenario tree (Martin et al., 2007a). The CSeU of the surveillance design of the official and private program could then be compared. Spreadsheets were created in Microsoft Excel 2010 to represent each surveillance design. The corresponding scenario trees are illustrated in Figs. 1–3. In the

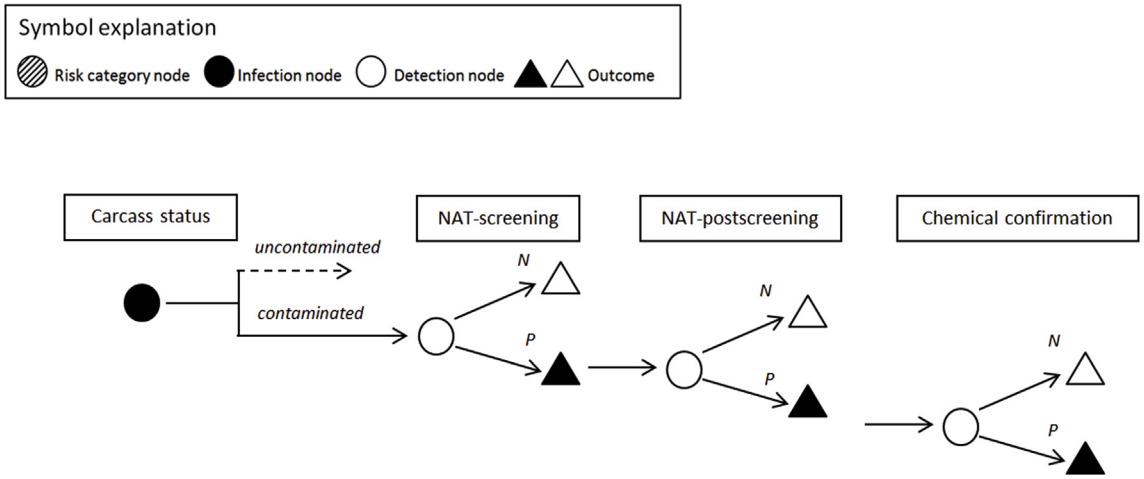


**Fig. 1.** Scenario tree illustrating the surveillance system for detecting residues of antimicrobials in carcasses of finisher pigs in a random surveillance design (with N meaning negative and P meaning positive).

random design (Fig. 1), it was assumed that the carcasses that need to be examined for presence of antimicrobial residues are selected randomly from all finishing pigs slaughtered in a year. By doing so, the proportion of pigs in the sample that originate from high-risk populations is the same as the proportion in the overall population of slaughtered pigs. In the risk-based design, a model was developed with the prevalence of chronic pleuritis or pneumonia in the herd of origin as risk category node (Fig. 2) and a model that, in addition, included the route of administration of antimicrobials (oral or parenteral, i.e. intramuscular or subcutaneous injections) as a risk category node (Fig. 3). The first model represents the risk-based sampling strategy that is currently applied in the private program. The latter represents a hypothetical alternative, as it is suggested that pigs injected with antimicrobials test positive for residues more often than orally medicated pigs (Berends, van den Bogaard, Van Knapen, & Snijders, 2001), as a result of a higher absorption into the body related to parenterally administered antimicrobials compared to orally administered antimicrobials, which are only partly absorbed from the gastro-intestinal tract (Mevius et al., 1989). As the specific treatment history of pigs is unknown at slaughter (in terms of route of administration of administered antimicrobials), skin lesions resembling injection sites were used as an indicator of parenteral administration of antimicrobials.

### 2.2.2. Input parameters

Distributions for input parameters were chosen to take into account uncertainty and variability, and were based on literature or expert opinion (Table 1). The outcome of each scenario tree model (CSeU) is the probability of detecting a contaminated carcass given that contamination with antimicrobial residues is prevalent at the level of the design prevalence. As EU legislation does not provide suggestions for design prevalence, two estimates were chosen for this study. An estimate of the true prevalence of residues of antimicrobials in finishing pigs of 0.01% was used, based on Danish finishing pig surveillance for the time period 2005–2009 (Baptista, Alban, Olsen, Petersen, & Toft, 2012) ('design prevalence A'). As a second estimate, the minimal prevalence level that is needed to detect at least one contaminated carcass with 95% confidence using the sample size laid down by EU legislation was used. This is 0.22% when 1350 out of 15,000,000 pigs are sampled yearly (Win Episcope 2.0 – Thrusfield, Ortega, de Blas, Noordhuizen, & Frankena, 2001) ('design prevalence B'). A relative risk of 3.2 was used to take a high within-herd prevalence of chronic pleuritis or pneumonia into account as risk factor, based on a pilot study described by Jelsma, Lesuis, and Ronteltap (2006). They described a 3.2 times higher probability of finding antimicrobial residues in carcasses from herds that had exceeded the level of lesions in the lungs and/or pleura by more than two times compared to the slaughterhouse average. The

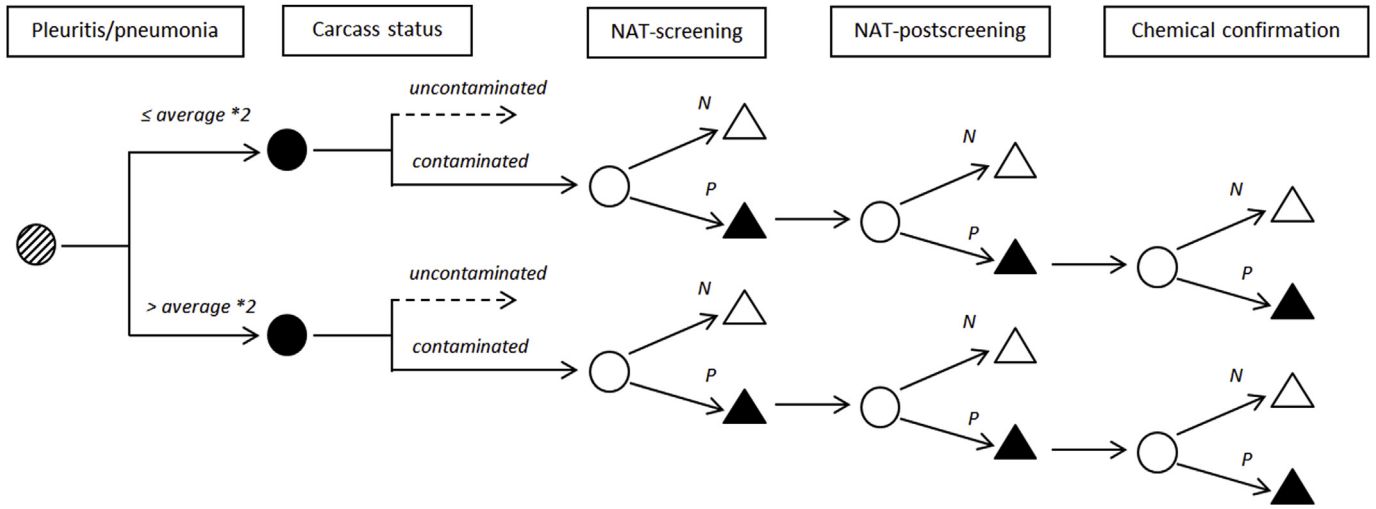


**Fig. 2.** Scenario tree illustrating the surveillance system for detecting residues of antimicrobials in carcasses of finisher pigs in a risk-based surveillance design, with the prevalence of chronic pleuritis and pneumonia in the herd of origin as risk category node (with N meaning negative and P meaning positive).

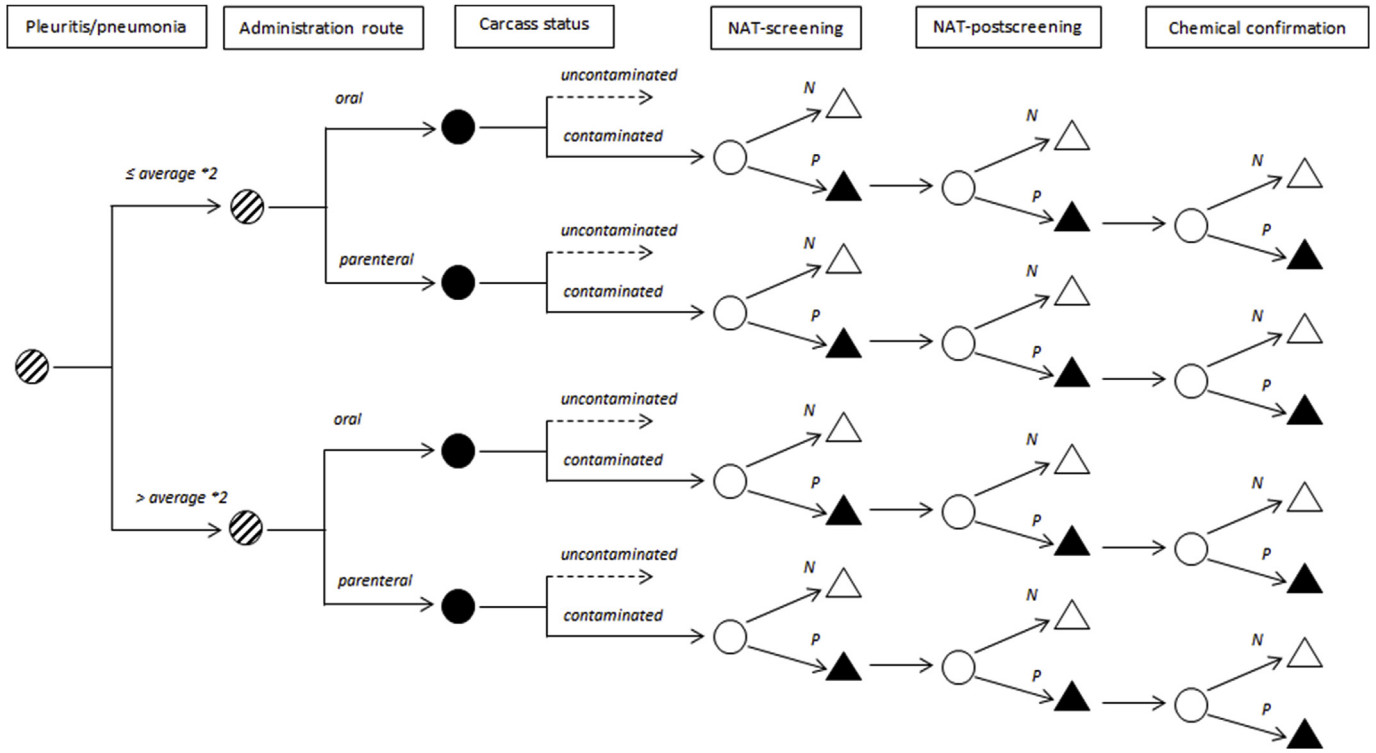


**Fig. 3.** Scenario tree illustrating the surveillance system for detecting residues of antimicrobials in carcasses of finisher pigs in a risk-based surveillance design, with the prevalence of chronic pleuritis and pneumonia in the herd of origin and the route of administration of antimicrobials as risk category nodes (with N meaning negative and P meaning positive).

**Table 1**
Input parameters used in the scenario tree models to detect antimicrobial residues in finishing pigs in the Netherlands, with description, value and source.

| Description of input parameter | Value | Source |
|---|---|---|
| Design prevalence A: true prevalence of residues | 0.01% | Baptista et al. (2012) |
| Design prevalence B: detectable prevalence | 0.22% | n.a. |
| Mean number of carcasses tested per year in official program | 2451 | NVWA, unpublished data |
| Mean number of carcasses tested per year in private program | 6992 | Vion, unpublished data |
| Risk factors and corresponding proportions | | |
| Relative risk of residues in carcasses from herds with high within-herd prevalence of chronic pleuritis and pneumonia | 3.2 | Jelsma et al. (2006) |
| Population proportion of carcasses from herds with high within-herd prevalence of chronic pleuritis and pneumonia | 25% | Bondt et al. (2004) |
| Surveillance proportion of carcasses from herds with high within-herd prevalence of chronic pleuritis and pneumonia, in private surveillance design | 100% | D. Oorburg, pers. comm. |
| Relative risk of injectables versus orally administrated antimicrobials | 2.6 | Berends et al. (2001) |
| Proportion of antimicrobials that is administered parenteral to finisher pigs between 2013 and 2015 | *RiskUniform* (14.3%; 17.5%) | SDa (2014), SDa (2015), SDa (2016) |
| Probability that herd has used antimicrobials during fattening period | *RiskUniform* (76.7%; 82.6%) | SDa (2014), SDa (2015), SDa (2016) |
| Surveillance proportion of finisher pigs with lesions of injectables at slaughter, in private surveillance design | 20% | n.a. |
| Test sensitivities for microbial assays and chemical confirmation | | |
| NAT-screening on renal pelvis fluid | 0.99 | Pikkemaat et al. (2008), expert opinion |
| NAT-meat and NAT-kidney | 0.95 | Pikkemaat et al. (2009a; 2009b), expert opinion |
| HPLC LC-MS/MS | 1.00 | Expert opinion |

proportion of pigs with the chronic pleuritis/pneumonia risk factor in the surveillance sample, i.e. the surveillance proportion, was 100%, whereas the population proportion was assumed to be 25%. This population proportion is based on the meat inspection slaughterhouse average and other estimates from the Netherlands (Bondt et al., 2004). A relative risk of 2.6 was used to take the risk of injectables versus orally administrated antimicrobials into account, based on calculations made by Berends et al. (2001). Data regarding the amount and types of antimicrobials administered to finisher pigs in the Netherlands in 2014, 2015 and 2016 were used to estimate the proportion of finisher pigs in the population that has been treated with antimicrobials and the proportion of orally and parenterally administered antimicrobials given that the pig was treated (SDa, 2015; SDa, 2016; SDa, 2017). These figures resulted in a mean probability of 12.7% of a pig being treated by parenteral administration of antimicrobials (i.e. the population proportion of the route of administration risk factor). The hypothetical surveillance proportion of pigs with lesions of injectables in the surveillance sample was set at 20%, where it was assumed that all of the carcasses with skin lesions indicative of injectables were treated by parenteral administration of antimicrobials. In the scenario trees, relative risks were transformed to adjusted risks, combining the relative risk and the proportion of animals per risk stratum in the population, to

ensure that the average design prevalence was constant across all animals subjected to the testing protocol laid down in the tree. Test sensitivity was set at 99% and 95% for the NAT-screening and NAT-post-screening, respectively. Specificity was assumed to be perfect and sensitivity was considered to be constant for the five groups of antimicrobials (M. Pikkemaat, pers. comm.). For chemical confirmation, test sensitivity and specificity were assumed to be perfect (Table 1).

#### 2.2.3. Model output

The models were developed using @RISK 6.2.1 (Palisade Corporation) in Microsoft Excel and outputs were based on 10,000 iterations, which appeared sufficient to obtain stable output values (mean and variance; results not shown). The number of detected cases above MRL as estimated by the models was compared with actual numbers of cases from the Dutch surveillance system over the years 2012–2015.

### 2.3. Economic evaluation

The costs of each design, expressed as the yearly costs for screening and subsequent confirmation of positive samples, were computed to economically evaluate and compare the random and risk-based surveillance designs. The mean number of carcasses tested per year in the official program (2,451) was assumed for each design. First, the expected number of NAT-screening, NAT-postscreening and chemical confirmation tests was calculated for each design, using the probabilities of the corresponding branches and limbs of the trees. Exact costs of each test were not publically available, yet the ratio of costs between NAT-screening, NAT-postscreening and HPLC LC-MS/MS in the Netherlands is currently known to be 1:2:20 (M. Pikkemaat, pers. comm.). Using this ratio, assumed costs per test were €10,- for NAT-screening, €20,- for NAT-postscreening and €200,- for chemical confirmation.

## 3. Results

Results per surveillance design are shown in Table 2. The probability that a carcass will yield a positive outcome when subjected to the testing protocol (CSeU), was 0.009% in the random surveillance design when the true prevalence of residues (0.01%) was used as design prevalence. The risk-based surveillance design based on the pleuritis/pneumonia risk factor yielded a CSeU that was twice as high (0.019%). With the addition of the risk factor on the route of administration the CSeU further increased to 0.021%. When the detectable prevalence of residues (0.22%) was used as design prevalence, CSeU varied from 0.207% in the random design to 0.429% and 0.471% in the risk-based designs. The estimated total costs for testing varied marginally between the surveillance designs, irrespective of design prevalence used, from €24,561 per year in the random design using design prevalence A to €24,858 in the risk-based design with the pleuritis/pneumonia and route of administration risk factors. (Table 2).

Between 2012 and 2015, a yearly number of zero to nine confirmed cases of carcasses with antimicrobial residues above MRL were found in the official program covering all pig slaughterhouses (NVWA, unpublished data). The model estimated the average number of cases to be 0.2 per year with design prevalence A and 5.1 per year with design prevalence B (Table 2). In the private program, a yearly number of five to six confirmed cases of carcasses with antimicrobial residues above MRL were found between 2012 and 2015 (Vion, unpublished data). The model for the risk-based design with the pleuritis/pneumonia risk factor estimated the average number to be 0.5 per year with design prevalence A and 10.5 per year with design prevalence B. It is important to note that the yearly sample size in the private program is nearly three times larger than the sample size of the official program (Table 1). With the actual sample size of the private program, the model for the risk-based design with the pleuritis/pneumonia risk factor estimated an average of 1.4 cases of carcasses with antimicrobial residues above MRL per year with design prevalence A and 30.0 per year with design prevalence B.

## 4. Discussion

EU Member States must implement residue monitoring plans to detect the illegal use or misuse of veterinary medicines in food producing animals and investigate the reasons for residue violations. In this study, the epidemiological performance of a random and risk-based sampling design of the surveillance program to detect residues of antimicrobials in finishing pigs was quantified using scenario tree modelling.

Results showed that the sensitivity to detect a residue-positive carcass doubled when surveillance was targeted at pigs originating from herds with a high prevalence of chronic pleuritis and pneumonia (compared to random sampling), at similar costs of testing. This is the result of the pleuritis/pneumonia risk category node in the scenario tree model, in which a relative risk of 3.2 was assumed. A validation of this parameter would require a comparison of the prevalence of pleuritis and pneumonia between herds with violated levels of residues and herds without residues. In Denmark, an investigation of eight finisher

**Table 2**
Mean sensitivities at unit level (CSeU), estimated number of confirmed positive carcasses per year, estimated total costs per year and true number of confirmed positive carcasses per year, for random and risk-based surveillance designs to detect antimicrobial residues in finishing pigs in the Netherlands.

| | Random design | Risk-based design | |
|---|---|---|---|
| | | Pleuritis/pneumonia prevalence | Pleuritis/pneumonia prevalence + route of administration of antimicrobials |
| True annual number of confirmed positive carcasses 2012–2015 (range)[a] | 0–9 | 5–6[b] | n.a. |
| *Design prevalence A (true prevalence of residues: 0.01%)* | | | |
| CSeU (%) | 0.009 | 0.019 | 0.021 |
| Number of confirmed positive carcasses[a] | 0.2 | 0.5[c] | 0.5[d] |
| Total costs (€) | 24,561 | 24,616 | 24,626 |
| *Design prevalence B (detectable mean prevalence: 0.22%)* | | | |
| CSeU (%) | 0.207 | 0.429 | 0.471 |
| Number of confirmed positive carcasses[a] | 5.1 | 10.5[c] | 11.5[d] |
| Total costs (€) | 25,631 | 26,834 | 27,061 |

[a] Yearly number of carcasses with residues present above MRL.
[b] Following a mean sample size of 6992 carcasses per year.
[c] Results when actual sample size of private program was applied: 1.4 (with design prevalence A) and 30.0 (with design prevalence B).
[d] Results when actual sample size of private program was applied: 1.5 (with design prevalence A) and 33.1 (with design prevalence B).

pig herds with a residue violation in the years 2010–2012 showed that on average the herd-level prevalence of chronic pleuritis was indeed higher than the abattoir average at the time of the residue violation (Alban et al., 2014). Our study indicated that the risk-based design is a more cost-effective approach than random sampling. Nevertheless, sensitivity values at unit level remained extremely low (< 0.5%) in both designs yet in agreement with the design prevalence used as input. Extending the risk-based design with the administration route of antimicrobials – via visual inspection of skin lesions indicative of injectables - as an additional risk factor led to a negligible increase in sensitivity. This can be explained by the low proportion of pigs with lesions of injectables in the hypothetical surveillance sample (20%), whereas our model assumes that 100% of the pigs with the pleuritis/pneumonia risk factor are targeted. In addition, it might be challenging to select a sufficient number of carcasses with lesions of injectables to reach a surveillance proportion of 20% within a satisfactorily large surveillance sample, as the prevalence of lesions of injectables is suggested to be low in finishing pigs (Berends et al., 2001; R. Herbes, pers. comm.). Another risk factor that could be included in a risk-based design is the stratification of surveillance for sows and finishing pigs. In the Netherlands, more (parenteral administered) antimicrobials are used in sows compared to finishing pigs (SDa, 2017), which might increase the probability of finding residues of antimicrobials. In Denmark, antibacterial residue prevalence was found to be 12–26 times higher in sows compared to finishing pigs (Baptista et al., 2012). As an explanation for this, it was suggested that the date of slaughter is less predictable for sows compared to finishing pigs and therefore more errors and incorrect identification of treated animals are being made. In agreement with our results, risk-based sampling based on a high within-herd prevalence of chronic pleuritis also resulted in detection of more residue cases in pork with higher cost-effectiveness than random monitoring in Denmark (Alban, Rugbjerg, Petersen, & Nielsen, 2016). Alban et al. also concluded that the costlier HPLC LC–MS/MS can replace the bioassay as a diagnostic method for antimicrobial residues in finishing pigs without an increase in total costs, if risk-based sampling is applied and the number of samples are reduced. Presi et al. (2008) demonstrated that risk-based sampling of slaughtered calves in Switzerland could increase the efficiency of detection of tetracycline residues by up to 100% compared to simple random sampling. Surprisingly, EU legislation does not demand separate reporting of results of random and risk-based sampling in residue surveillance, which may discourage EU Member States to implement risk-based sampling. It is therefore suggested to report results from risk-based and random sampling separately (Alban et al., 2018).

The sampling strategy of the official program was considered random in this study, although in practice it is a combination of random and risk-based sampling. This assumption has likely led to an underestimation of the sensitivity of the official program. The true prevalence of residues of antimicrobials in finishing pigs in the Netherlands is unknown. Using an estimate of 0.01%, the model estimated a number of cases with residues above MRL that is lower than the observed number obtained from actual surveillance data. Contrary, using a design prevalence of 0.22% led to an seemingly overestimation of cases with residues above MRL, indicating that the true prevalence of carcasses with residues above MRL in the Netherlands must lay somewhere between 0.01% and 0.22%. Nevertheless, in a best-case scenario, assuming a true prevalence of 0.01%, it is expected that on a yearly basis 1500 of out 15,000,000 slaughtered finishing pigs will contain residues of antimicrobials above MRL. It is unknown, however, which amounts of residues of antimicrobials actually reach the consumer, and if so, to which extent it would lead to clinically apparent effects (Berends et al., 2001). These substances are often legal antimicrobials which are in many cases also used for treatment of humans. It would be extremely costly if the surveillance program should aim for detecting each of these cases. Moreover, human cases are only seldom reported (Alban et al., 2018; Berends et al., 2001). Therefore, residue surveillance is seen as a way to demonstrate compliance with legislation and where herds that structurally violate withdrawal periods are identified. To be effective in reducing risks of MRL exceedance, such herds should be followed-up for a root-cause analysis, followed by implementation of preventive measures by the farmer. That is currently practice in the abattoir in charge of the private program described in this study, where farms that deliver pigs whose samples exceed the MRL in the monitoring are put on hold until preventive measures are proposed to the abattoir and implemented on the farm. This implies that to avoid being put on hold acts as an incentive for producers to comply with the withdrawal times.

Applying an entirely risk-based design will marginally increase the costs for diagnostic testing compared to random testing, because the number of samples taken as part of the screening and the costs per sample were kept constant in all scenarios. In Denmark, the application of a risk-based design lead to a reduction of the number of samples to be taken (Alban et al., 2016). The total costs of a surveillance program also include intervention and follow-up costs. It would be interesting to relate these costs to the benefits gained from an increase in sensitivity, such as a reduction in costs of error (e.g. trade restrictions imposed by third countries following residue violations and other economic consequences of false negative results) and the preventative effect against misuse of antimicrobials.

Finally, even though risk-based sampling appears to be the favoured approach in terms of epidemiological performance, sampling only pigs from high-risk herds is undesirable as a large fraction of the population will then be missed. As suggested by Alban et al. (2016), this may result in some farmers losing the incentive to comply with withdrawal periods and there might be reasons for finding residues other than a high within-herd prevalence of chronic pleuritis/pneumonia or parenteral administration of antimicrobials.

## 5. Conclusion

The results of this study provided a comparison of two surveillance designs – random versus risk-based - that could be used to monitor residues of antimicrobials in finishing pigs. Such an assessment of various surveillance designs could be highly useful to support decision-making towards optimizing surveillance of food-borne hazards in terms of costs and sensitivity. In this study, risk-based alternatives to random sampling improved the cost-effectiveness of residue surveillance in slaughter pigs in the Netherlands, which could be used to enhance current programs and to increase awareness in food business operators. Also, it is likely that residue surveillance sensitivity will vary between countries, yet it is unknown to what extent. This paper contributes to the quantification of residue surveillance sensitivity and therefore comparison between countries, which will benefit trade.

## Acknowledgements

The following persons are acknowledged for input during the project: Martijn Bouwknegt (Vion), Sanne van der Voorde and Rik Herbes (Netherlands Food Safety Authority), Mariël Pikkemaat (RIKILT Research Institute) and Jobke van Hout (GD Animal Health). Also, the entire SANTERO project group is acknowledged for inspiring discussions during the project. This work was funded through the Animal Health and Welfare ERA-NET consortium (https://www.anihwa.eu/) under the SANTERO project, with special thanks to the Ministry of Economic Affairs, the Netherlands.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.foodcont.2018.11.022.

## References


Alban, L., Léger, A., Veldhuis, A., & Van Schaik, G. (2018). Modernizing the antimicrobial residue monitoring programs for pig meat in Europe – the balance between flexibility and harmonization. *Food Control, 86*, 403–414.

Alban, L., Pacheco, G., & Petersen, J. V. (2014). Risk-based surveillance of antimicrobial residues in pigs – identification of potential risk indicators. *Preventive Veterinary Medicine, 114*, 88–95.

Alban, L., Rugbjerg, H., Petersen, J. V., & Nielsen, L. R. (2016). Comparison of risk-based versus random sampling in the monitoring of antimicrobial residues in Danish finishing pigs. *Preventive Veterinary Medicine, 128*, 87–94.

Anonymous (1996). *Council Directive 96/23/EC of 29 April 1996 on measures to monitor certain substances and residues thereof in live animals and animal products.* The EU Commissionhttp://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1996:125:0010:0032:EN:PDF.

Baptista, F. M., Alban, L., Olsen, A. M., Petersen, J. V., & Toft, N. (2012). Evaluation of the antibacterial residue surveillance programme in Danish pigs using Bayesian methods. *Preventive Veterinary Medicine, 106*, 308–314.

Berends, B. R., van den Bogaard, A. E. J. M., Van Knapen, F., & Snijders, J. M. A. (2001). Veterinary public health: Human health hazards associated with the administration of antimicrobials to slaughter animals. *Veterinary Quarterly, 23*, 2–10.

Bondt, N., Van den Elzen, D., Hoste, R., Van Wagenberg, C., Vermeij, I., & Van der Fels, B. (2004). *Terugdringen van slachtafwijkingen in de Varkensvleesketen (report in Dutch). Report 5.04.04, LEI, Den Haag.* Retrieved from http://edepot.wur.nl/89667.

EFSA (2016). *Report for 2014 on the results from the monitoring of veterinary medicinal product residues and other substances in live animals and animal products*EFSA Supporting publication70. 2016:EN-923 http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2016.EN-923/epdf.

European Commission (EC) (2003). Reflection Paper on Residues in foodstuffs of animal origin. Retrieved from https://ec.europa.eu/health/veterinary-use/maximum-residue-limits/reflection-paper_en.

Jelsma, A., Lesuis, R., & Ronteltap, E. (2006). *Final report on the data analysis from the visual inspection pilot.* Dutch Food and Consumer Product Safety Authority36.

Katz, S. E. (1980). Antimicrobial residues and resistant organisms: Their occurrence, significance, and stability. *The effects on human health of subtherapeutic use of antimicrobials in animal feeds. Ed. By: Committee to study the human health effects of subtherapeutic antibiotic use in animal feeds. National Academies Press (US)*Washington DC: Office of Publications Nat Acad Sci 1980.

Martin, P. A., Cameron, A. R., & Greiner, M. (2007a). Demonstrating freedom from disease using multiple complex data sources 1: A new methodology based on scenario trees. *Preventive Veterinary Medicine, 79*, 71–97.

Martin, P. A., Cameron, A. R., & Greiner, M. (2007b). Demonstrating freedom from disease using multiple complex data sources 2: Case study – classical swine fever in Denmark. *Preventive Veterinary Medicine, 79*, 98–115.

Mevius, D. J., Vellenga, L., Breukink, H. J., Nouws, J. F. M., Vree, T. B., & Driessens, F. (1989). Pharmacokinetics and renal clearance of oxytetracycline in piglets following intravenous and oral administration. *Veterinary Quarterly, 8*, 274–284.

Pikkemaat, M. G., Oostra-van Dijk, S., Schouten, J., Rapallini, M., Kortenhoeven, L., & van Egmond, H. J. (2009b). Nouws antibiotic test: Validation of a post-screening method for antibiotic residues in kidney. *Food Control, 20*, 771–777.

Pikkemaat, M. G., Oostra-van Dijk, S., Schouten, S., Rapallini, M., & van Egmond, H. J. (2008). A new microbial screening method for the detection of antimicrobial residues in slaughter animals: The Nouws antibiotic test (NAT screening). *Food Control, 19*, 781–789.

Pikkemaat, M. G., Rapallini, M. L. B. A., Oostra-van Dijk, S., & Elferink, J. W. A. (2009a). Comparison of three microbial screening methods for antibiotics using routine monitoring samples. *Analytica Chimica Acta, 637*, 298–304.

Presi, P., Stärk, K. D. C., Knopf, L., Breidenbach, E., Sanaa, M., Frey, J., et al. (2008). Efficiency of risk-based vs. random sampling for the monitoring of tetracycline residues in slaughtered calves in Switzerland. *Food Additives & Contaminants Part a Chemistry, Analysis, Control, Exposure and Risk Assessment, 25*, 566–573.

SDa, the Netherlands Veterinary Medicines Institute (2015). Usage of antibiotics in agricultural livestock in The Netherlands in 2014. Retrieved from http://www.autoriteitdiergeneesmiddelen.nl/en/publications.

SDa, the Netherlands Veterinary Medicines Institute (2016). Usage of antibiotics in agricultural livestock in The Netherlands in 2015. Retrieved from http://www.autoriteitdiergeneesmiddelen.nl/en/publications.

SDa, the Netherlands Veterinary Medicines Institute (2017). Usage of antibiotics in agricultural livestock in The Netherlands in 2016. Retrieved from http://www.autoriteitdiergeneesmiddelen.nl/en/publications.

Stärk, K. D. C., Regula, G., Hernandez, J., Knopf, L., Fuchs, K., Morris, R. S., et al. (2006). Concepts for risk-based surveillance in the field of veterinary medicine and veterinary public health: Review of current approaches. *BMC Health Services Research, 6*, 20.

Thrusfield, M., Ortega, C., de Blas, I., Noordhuizen, J. P., & Frankena, K. (2001). WIN EPISCOPE 2.0: Improved epidemiological software for veterinary medicine. *The Veterinary Record, 148*, 567–572.


## Further reading


Anonymous (1998). *Commission Decision 98/179 of 23 February 1998 laying down detailed rules on official sampling for the monitoring of certain substances and residues thereof in live animals and animal products.* The EU Commission4. http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31998D0179&from=EN.