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Modernizing the antimicrobial residue monitoring programs for pig meat in Europe – The balance between flexibility and harmonization

Lis Alban [a, *], Anaïs Léger [b], Anouk Veldhuis [c], Gerdien van Schaik [c, d]

[a] Danish Agriculture & Food Council, Copenhagen, Denmark
[b] SAFOSO, Bern, Switzerland
[c] GD Animal Health, Deventer, The Netherlands
[d] Utrecht University, The Netherlands

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ABSTRACT

The EU Residue Directive is currently being renegotiated. One key question is how to balance flexibility and harmonization. To address this, we reviewed Danish, Dutch and Swiss monitoring programs for antimicrobial residues in pig meat using the recently developed RISKSUR design tool. The results identified variation regarding number of surveillance components, reactions to suspect and positive findings, prevention activities, diagnostic method, sample matrix, use of targeted/risk-based approaches, and sampling frequency. This variability could largely be explained by differences in overall surveillance objective: Denmark and the Netherlands have a large pork export and higher need for documenting compliance with legislation, whereas Switzerland only trading with EU has a lower need for spending resources on monitoring. It is recommended that the future EU Directive should set standards for monitoring to ensure a basic level of monitoring enabling comparison of results. Minimum handling of carcasses with residues above maximum residue level should be harmonized. Risk-based sampling should be encouraged, and results from risk-based and random sampling should be reported separately. Harmonization is unnecessary for number of surveillance components (but a private component is recommended), prevention, diagnostic method, and way of sampling – assuming that the diagnostic method and sampling matrix combination have sufficient validity.

1. Introduction

The consequence of human exposure related to consumption of meat with residues originating from veterinary medicinals with an antibacterial effect may be considered limited, because of the low level of residues resulting in very few, acute human cases, and symptoms are usually mild, if seen at all (Tscheuschner, 1972; Berends, van den Bogaard, Van Knapen, & Snijders, 2001; Baptista, Alban, Olsen, & Petersen, 2010). The most serious may be considered allergic reaction to penicillin, where symptoms include rashes, hives, itchy eyes, and swollen lips, tongue or face. Treatment with corticosteroids has shown to be successful in those cases (Tscheuschner, 1972). Long-term exposure or repeated exposures might result in disturbance of the intestinal microbiota, whereas single exposures are not considered to be able to induce such turbulence (Berends et al., 2001). In all cases, consumers perceive presence of residues of e.g. antimicrobials in food products as indeed unwanted. Three out of 10 Europeans mentioned chemical residues from pesticides (31%), antibiotics (30%) and pollutants like mercury and dioxins (29%) as risk to be "very worried" about - according to a European survey about consumer perception about food safety (TNS, 2010).

To secure consumer confidence and trade, actions must be taken to prevent presence of residues of antimicrobials in meat. Monitoring of meat can be interpreted as an evaluation of the compliance of the actions taken earlier in the supply chain; a high prevalence will indicate that compliance is low, whereas a low prevalence will indicate that compliance is high. Findings of residues in meat at border inspection may result in rejection of the import on certain markets (Alban, Rugbjerg, Petersen, & Nielsen, 2016).

The current legislation regulating the area of residues in meat within the European Union (EU) originates from 1996 and is called EU Directive 96/23/EC. This Directive requires EU Member States to

* Corresponding author.
E-mail address: lia@lf.dk (L. Alban).

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implement a national residue monitoring plan for residues. It describes the minimum requirements for official sampling frequency for specific groups of residues among livestock in a country (The Council for the European Communities, 1996). Accordingly, 0.05% of the pigs produced are to be checked for all kinds of residues through official sampling. Among these, 0.03% are checked for veterinary drugs and contaminants (Group B substances), and again, 0.01–0.02% are checked for drugs with antibacterial effect (Group B1 covering antibiotics and sulphonamides – in the following called antimicrobials). The remaining 0.02% of the samples are analysed for substances, which have an anabolic effect and prohibited substances (Group A substances). A minimum of 5% of these samples are analysed for Group A6, which covers prohibited veterinary substances including among others chloramphenicol, chlorpromazine, metronidazole and nitrofurans. A MRL cannot be established for these substances (The EU Commission, 2010).

Presence of residues of prohibited substances is monitored either in live animals on the farm or in various animal tissues (including meat) at the slaughterhouse. Residues of antimicrobials are monitored only in relation to slaughter, where the matrix is target animal tissue/fluid or meat. Furthermore, the Directive lays down the framework for the reporting of information from monitoring. In line, EU Regulation 37/2010 establishes maximum limits for residues (MRL) of veterinary medicinal products in food-producing animals and animal products (The EU Commission, 2010).

According to Directive 2001/82/EC marketing authorization for veterinary medicinal can be granted either via a national, a decentralized, a mutual recognition or a central procedure (The EU Commission, 2001). All MRL values are determined at the central level by the European Medicines Agency's Committee for Medicinal Products for Veterinary Use (CVMP). The withdrawal period is determined through the MRL value for the substances (e.g. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/q_and_a/q_and_a_detail_000039.jsp) and a residue depletion study as described in the Guideline "Approach towards harmonization of withdrawal periods" (EMEA/CVMP/036/95). There may be differences in length of the withdrawal period between Member States due to individual interpretation of the residue depletion studies, if the product has been approved via national procedures. CVMP has the faculty to harmonize withdrawal periods via article 34 in Directive 2001/82, if considered necessary. Systematic compliance with withdrawal periods cannot be controlled easily, as it would require control visits to the individual herds during which recordings of use of antimicrobials are compared with dates of delivery of animals to slaughter. Therefore, to ensure feasibility focus is on the presence of residues in the meat at the time of slaughter.

The aim of the existing residue legislation is to harmonize the control of residues in the Member States, thus ensuring a high level of health protection, while avoiding disruption in intra-Community trade (The EU Commission, 2003). The national residue monitoring plans were not designed originally to assess general consumer exposure to residues, but to reinforce supervision and monitoring of illegal use of pharmacologically active substances as stated in EU Directive 85/358 (The Council for the European Communities, 1985). The EU Directive 96/23 will be repealed by December 14, 2019 (EU Commission Residue Working Group, 2017a); this implies that negotiations about a new legislation will take place from now until 2019. The aim is to have a transparent and simplified legislation. A reflection paper about this issue was developed by the EU Commission in (2003). According to this document, the overall goal is to determine new means to balance consumer protection, animal health, welfare and trade requirements (The EU Commission, 2003). Ideally, the coming legislation should be flexible, so it can reflect the level of need for monitoring in the individual Member States, while still having sufficient harmonization to avoid disruption of trade. Moreover, risks may shift over time. Therefore, a flexible framework based upon risk-based sampling should be aimed for to support the most effective method of detection and control of illegal/wrong use of antimicrobials and other veterinary substances (The EU Commission, 2003).

In 2014, 15 Member States reported a total of 46,023 official samples tested for one or more antimicrobial substances in pig meat among which 74 were non-compliant samples. The most commonly found antimicrobial class consisted of tetracyclines including chlortetracycline, doxycycline, and oxytetracycline which represented 32 out of the 74 samples (with 77 non-compliant results). Other substances found included amoxycillin (N = 2), benzylpenicillin and other penicillins (N = 4), ciprofloxacin (N = 1), dihydrosteptomycin (N = 9), enrofloxacin (N = 3), florfenicol (N = 1), gentamycin (N = 1), lincomycin (N = 3), substances containing sulfa (N = 18), trimethoprim (N = 4) and tularthromycin (N = 1). Moreover, 26,541 samples were tested for presence of prohibited substances (Group A6) for which there is a zero tolerance; here one sample was positive for chloramphenicol and two were positive for metronidazole/hydroxymetronidazole (EFSA, 2016). Hence, a substantial number of samples are tested for residues of antimicrobials in livestock products and only very few are found positive each year in the EU.

Monitoring data can be used to document a low prevalence of residues of antimicrobial origin. A distinction is here made between monitoring and surveillance. Monitoring is defined as a data collection, which is not linked with actions related to a positive finding or a prevalence above a certain threshold. This is contrary to surveillance, where actions are clearly defined (Hoinville et al., 2013). In the case of residues, the routine sampling may be considered monitoring, because the meat is already distributed on the market unless carcasses are withheld during testing. Still, positive findings require postponed action, which is an element of surveillance. When the dimensioning of a surveillance program is planned, it is important to identify the expected cost of error, which in the case of antimicrobial residues may be defined as the probability of missing one or more cases times the economic consequences of this (adapted after Cameron, 2012). As stated above, importing countries may react negative to finding residues of antimicrobials in imported meat. In the worst case, this may imply that exports from a country may be denied for months, leading to substantial costs. Based upon this, it may be hypothesized that the surveillance objectives may vary between countries in the sense that A country, which is exporting meat, may have a higher need for in-country up-to-date monitoring data compared to a country with no export or a country importing meat. Other factors might also influence – such as risk perception regarding presence of residues.

Trading partners and consumers demand meat with a documented low prevalence of residues. However, sampling is associated with costs, and the veterinary authorities are responsible for a variety of monitoring and surveillance programs, making it necessary to prioritize carefully the need for and ways of sampling. Risk-based sampling may represent a way of improving the cost-effectiveness; if animals or herds with an increased probability of the condition of interest are sampled, a higher number of positive cases may be found compared with representative (random) sampling. This may result in a higher efficiency of the system without loss of efficacy (Stärk et al., 2006). Two recent studies from Denmark have shown that the cost-effectiveness of a residue surveillance program in slaughter pigs could be improved by increasing the sampling frequency in high-risk herds compared to random sampling. High-risk herds were defined as finisher pig herds with a within-herd prevalence of chronic pleuritis twice as high or higher than the average (Alban et al., 2014, 2016). The

outcome of these two studies was used when designing the new Danish private program involving risk-based sampling, covering finishers in Denmark (Alban, 2017; Alban et al., 2016). The private program is paid by the abattoirs and acts on top of the public program.

Traditionally, a variety of biological methods have been used for residue monitoring, sometimes alone and sometimes in combination with a chemical test, where the latter is used to confirm the kind of substance found and to quantify the exact amounts present. Their advantages are that they are cheap and the sensitivity is believed to be acceptable, when the quantitative level of residues is close to the MRL (Pikkemaat, Rapallini, Oostra-van Dijk, & Alexander Elferink, 2009). New chemical diagnostic methods for detection of residues are becoming cheaper, allowing their use in routine monitoring. These methods – such as HPLC LC/MS-MS - have a very high sensitivity and specificity and can provide results of a plethora of substances concurrently. But they are still associated with higher costs than the biological methods (Alban et al., 2016).

EFSA has been assigned the tasks of examining the data collected and preparing reports on the results obtained from monitoring (EFSA, 2015). However, the monitoring data are reported in an aggregated format. This is punishing countries using targeted/risk-based principles or diagnostic methods with a high sensitivity such as HPLC LC/MS-MS for demonstrating an apparent higher risk compared to countries applying random sampling with a diagnostic test with lower sensitivity.

Hence, several questions need to be addressed to identify recommendations for a cost-effective monitoring program and new, targeted legislation. In this paper, we have addressed a number of aspects (called key attributes) related to the design of residue monitoring programs: surveillance objective and expected outcome, number of surveillance components, actions taken upon suspect or positive findings in monitoring, preventive actions taken prior to slaughter to avoid presence of residues of antimicrobials in pig meat, testing protocol (diagnostic method and sample matrix), study design (including sampling frequency), and sampling strategy (random or risk-based).

To do so, the monitoring programs for legal antimicrobials (Group B1) in pig meat of three European countries were described, highlighting differences and similarities. Use related to prohibited antimicrobials (Group A6) was only dealt with briefly.

The programs were divided into the official program and the abattoirs' own check – in the following named the official and the private program, respectively.

2. Materials and methods

2.1. Selection of countries and origin of data

The monitoring programs for residues of antimicrobial origin in Denmark, the Netherlands and Switzerland were selected for this study, representing a variety in size of pig production and export value, but all following EU legislation. Moreover, these countries represented a variety of coverage regarding the minimum sampling frequency defined in EU Directive 96/23 (higher than required in Denmark and the Netherlands, equal to the minimum requirement in Switzerland). Data were obtained through interviews with relevant stakeholders, reading the EU and national legislation, national reports, and EFSA reports. Relevant references arising from literature searches using Google and Scopus were shared between three case studies (of which this paper reports from the first) within the overall residue surveillance projects.

The review of the three monitoring programs – involving actions take in the supply chain from the swine producer to the abattoir - was structured according to the information obtained using a software tool developed by the RISK-based Animal Health SURveillance systems (RISKSUR) project. Please see more information about the RISKSUR project on: http://www.fp7-risksur.eu/.

2.2. Description of the monitoring programs using the RISKSUR design tool

The programs were described using the RISKSUR surveillance design tool. The tool, which was developed between 2012 and 2015 in a project funded by the Seventh Framework Program of the EU, guides persons in the development of animal health surveillance systems, with the aim of structuring the process of designing and documenting the surveillance program. By using the tool in the current study, its usefulness for applications outside animal health surveillance was evaluated.

The RISKSUR design tool reflects the sequence of steps involved in the development of a surveillance system. The user is provided with advice and information gathered from the literature and expert opinion, as well as links to relevant epidemiological sampling tools. The design tool also supports the re-design of existing surveillance systems, to increase performance targets such as sensitivity, timeliness, coverage, etc. By application of the design tool, the user is presented with an instrument that displays the surveillance decisions, which need to be made when designing a surveillance system. The design tool provides information for the user that helps to define the target hazard, identify the surveillance objective and expected outcome, surveillance components, handling of suspects and positive findings, preventive activities, testing protocol, study design, sampling strategy, sample collection, data/sample transfer and analyses (Fig. 1). In return, the design tool provides a review of the surveillance system that is evaluated by the user. The design tool is available online via the website http://www.fp7-risksur.eu.

2.3. SWOT analysis

A SWOT analysis implies an analysis of the strengths (S), weaknesses (W), opportunities (O) and threats (T). It is an approach designed to evaluate the planning and functioning of an activity in a structured manner – in this case the monitoring program for residues of antimicrobials in pig meat. It is developed through a brainstorm during which the strengths, weaknesses, opportunities and threats of the activity are identified. The strengths consist of the characteristics of the activity, which gives it an advantage, whereas the weaknesses are the characteristics, which place the activity at a disadvantage relative to other competitors. Opportunities are the elements in the environment which the activity could exploit to its advantage, and threats are the elements which could cause trouble for the activity. Hence, strengths and weaknesses deal with internal elements, whereas opportunities and threats deal with external elements (Dyson, 2004).

The SWOT analysis was inspired by a similar SWOT analysis about surveillance systems for pig health in the United Kingdom (Stärk & Nevel, 2009). The SWOT analyses were first made for each of the three countries by the author, who had used the RISKSUR design tool for that country specifically. Subsequently, these SWOT analyses were presented to different experts involved in the country's monitoring of antimicrobial residues for comments and corrections. For Denmark, this consisted of four experts, representing the largest abattoir company's laboratory, the national veterinary authority, the national veterinary laboratory, and the Danish Agriculture & Food Council, which is giving advice to the Danish meat industry. For the Netherlands, this consisted of one representative from the largest abattoir company and one

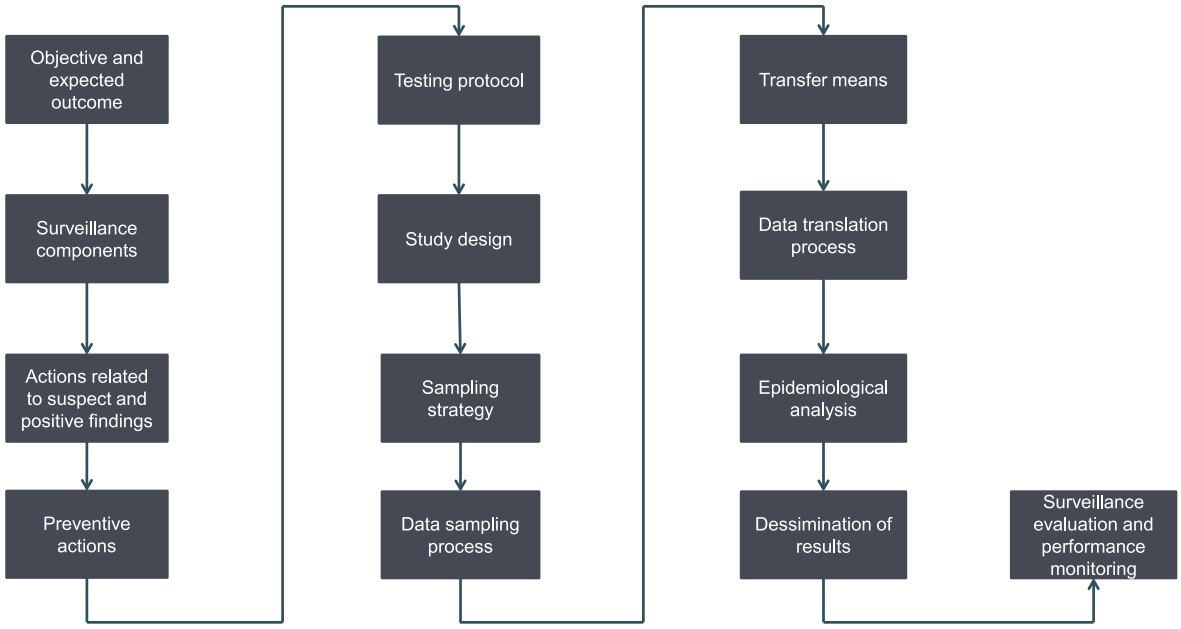

Fig. 1. Graphical description of the elements in the RISKSUR design tool. Source: http://webtools.fp7-risksur.eu.

representative from the national food safety authority. For Switzerland, this consisted of two representatives from the federal office in charge of the national programme.

3. Results

3.1. Differences and similarities between the programs

The key attributes of the three programs are summarized in Table 1. The three surveillance programs differed with respect to surveillance objective and expected outcome, number of surveillance components, actions taken upon suspect and positive findings in monitoring, preventive activities taken prior to slaughter to avoid presence of residues of antimicrobials in pig meat, testing protocol, study design, and sampling strategy (Table 1).

3.1.1. The Danish program

The surveillance program was initiated in 1972 by the Danish authorities, and focus was on meat and by-products from livestock as well as milk and eggs. For pigs, the matrix was kidney. Initially, a low number of samples were analysed, and any finding of residues was considered positive in the lack of a MRL (Danish Veterinary and Food Administration, 1972). For verifying compliance with export requirements raised by various countries outside the EU, Danish abattoirs have since 2001 randomly sampled sows and finishing pigs as part of a private surveillance program acting on top of the public program (Baptista, Alban, Olsen, Petersen, & Toft, 2012). The focus on residues may be interpreted as part of the long-term focus on reducing the use of antimicrobials and associated risk of development of antimicrobial resistance in Denmark as described by Temten, Kruse, Nielsen, Pedersen, and Alban (2016). However, the focus may also be seen as a genuine interest in avoiding presence of residues of antimicrobials specifically as reflected in an iconic graphic designed by the Danish artist Michael Witte in 1978 (https://da.wikipedia.org/wiki/Mikael_Witte).

Surveillance objective and expected outcome – The objective is to show to the EU that the legislation regarding MRL in pig meat is complied with through prevalence estimation. This may be used to show to consumers and trade partners that the prevalence of residues of antimicrobials is very low in pig meat. It may also be used to show to pig producers that the veterinary authorities and the Food Business Operator have focus on wrong or illegal use of veterinary medicinals in pig meat (Alban et al., 2016).

Number of surveillance components - The Danish programs for residues of antimicrobials involves four surveillance components: the official and the private program each have two components; one for sows/boars and one for finishing pigs (Alban et al., 2016).

Handling of suspects and positives - The programs are run as surveillance programmes implying that tested carcasses are withheld until a negative test result is made available. Moreover, a call to the farm will be made either in case the concentration of residues found is above MRL or if the concentration of tetracycline residues is above the MRL required by certain trade partners, which have a lower MRL than applied in EU. In the official programme, the call and the associated investigation will be undertaken by an official veterinarian from the Danish Veterinary and Food Administration. In the private program, a pig veterinarian employed by the Danish Agriculture & Food Council will undertake the investigation including an evaluation of the procedures in place on the farm. In line, subsequent delivery from the farm is blocked until a report on the cause of the residues and potential corrective actions have been made. In case the finding was below the MLR, an agronomist affiliated with the abattoir company contacts the swine producer to investigate/discuss reasons for the presence (Alban et al., 2014).

Actions taken to prevent presence of residues of antimicrobials in pig meat – A general recommendation about only using as little antimicrobials as possible but as much or often as needed is officially expressed in Denmark. This e.g. is reflected in the Yellow Card system, which sets limits to how much antimicrobials can be used in an age group (Alban, Dahl, Andreasen, Petersen, & Sandberg, 2013). Use of a private standard – called the Danish Product Standard - is widespread in Danish pig production (Knowledge center for Swine Production - SEGES, 2016). The Standard among others acts as an instrument to prevent residues from being present at the time of slaughter e.g. by requiring 30 days withdrawal time for tetracyclines. Moreover, other preventive activities are in place such as regular communication from the pig industry informing the pig producers about the risk associated with poor marking of

Table 1
Summary table highlighting key characteristics of the antimicrobial residue programs in Denmark, The Netherlands and Switzerland.

Characteristic	Denmark	The Netherlands	Switzerland
Size of production	18-20 mio. finishing pigs and 0.5 mio. sows/boars	15 million pigs slaughtered per year	2.7 million pigs slaughtered per year
Surveillance objective and target population	Controlling compliance[a] with MRLs for residues of veterinary medicinal products through estimation of prevalence. **Public program**: Both small and large slaughterhouses are targeted **Private program**: Abattoirs slaughtering <250 sows/boars or <1000 finishing pigs per year are not included	Controlling compliance[a] with MRLs for residues of veterinary medicinal products through estimation of prevalence. **Public program**: Both small and large slaughterhouses are targeted **Private program**: The largest abattoir company in NL	Controlling compliance[a] with MRLs for residues of veterinary medicinal products through estimation of prevalence. **Public program**: Both small and large slaughterhouses are targeted
Expected outcome	To demonstrate to consumers and trade partners outside the EU that the prevalence of residue in pig meat is negligible To show to pig producers that focus is on avoiding residues	To demonstrate to consumers and trade partners outside the EU that the prevalence of residue in pig meat is negligible To show to pig producers that focus is on avoiding residues	To fulfil EU legislation to enable trade in pig meat with the EU
Surveillance components	4 components – 2 official (sows/boars vs. finishing pigs) and 2 private (sows/boars vs. finishing pigs)	2 components – an official and a private	1 component – an official
Actions related to suspect and positives findings	Carcasses are withheld until result of testing is available. Positive carcasses are condemned	Carcasses are not withheld until result of testing in available.	Carcasses are not withheld until result of testing in available.
Preventive actions	Communication and control campaigns targeted producers at regular intervals regarding implications for export, correct marking of treated animals, correct injection techniques and recording of use of antimicrobials – several of these issues are part of the quality assurance	Quality assurance for trade partners, legal requirements	Legal requirement from EU, farmers' initiatives supported by vets to reduce their use of antimicrobial (and consequently potential residues in meat), non-compliance with the legislation might impact on individual trade with the two main Swiss food distributors
Testing protocol	**Diagnostic method**: Direct testing using HPLC LC-MS/MS **Matrix**: Meat. No pooling	**Diagnostic method**: Microbiological screening and confirmation by HPLC LC-MS/MS. **Matrix**: Pre-urine and kidney or meat fluid. No pooling	**Diagnostic method**: Non-harmonized testing at cantonal level using different biological and chemical diagnostic tests for screening and confirmation **Matrix**: muscle, liver, kidney. No pooling
Study design and sampling strategy	**Official/private program**: One-stage, random sampling. 20 times higher intensity in sow/boars compared to finishing pigs (=targeted) **Official program**: One-stage, random sampling in sows and boars **Private program**: Two-stage, risk-basedthrough higher sampling intensity in finishing pig herds with high prevalence of chronic pleurisy Random sampling of sows and boars	**Official program**: One-stage, random, sampling at the abattoir with 25% risk-based in an unstructured way **Private program:** One-stage, random sampling for sows/boars and two-stage, risk-based for finisher herds defined as herds with high prevalence of chronic pleurisy or pneumonia	**Official program**: In general one stage, random sampling at the abattoir. Operators are asked to target, if possible, susceptible animals based on their experience as well as on sex, age, species and production system
Data generation/sampling generation process	Sampling spread randomly throughout the year. Pre-planned for 1 year and continuous follow-up	Sampling spread randomly throughout the year.	Sampling spread randomly throughout the year.
Evaluation of performance	Continuous check of performance by laboratory technicians. Occasional discussions between lab, authority and abattoir about performance	Regular trend analyses conducted by the abattoir as part of the general risk assessment scheme.	No plan for the evaluation of performance.

[a] Including absence of use of prohibited substances.

treated animals and the usefulness of rubber bands etc. for marking of treated sows (Alban, 2017).

Testing protocol – The diagnostic method used is direct HPLC LC-MS/MS which allows for quantification of the concentration of residues also below the MRL (Alban et al., 2016).

In 2016, meat replaced kidneys as sample matrix (Alban et al., 2016).

Study design and sampling strategy - The testing frequency is 20 times higher in sows and boars compared to finishing pigs in both the official and the private program. This is due to a higher observed probability of finding residues in sows/boar. For three of the four components, sampling is at random. For sows and boars, 0.25% is tested in the official program and 1% is tested in the private program. For finishing pigs, around 0.01% is tested in the official program and 0.05% is tested in the private program. Since 2016, the own check program for finishing pigs has been risk-based, with 0.025% of the samples taken in high-risk herds and 0.025% at random (Danish Butchers' Association, 2015; Alban et al., 2016).

3.1.2. The Dutch program

The Dutch program is characterized by an official and a private program, where the latter is carried out by the largest abattoir company. Monitoring of residues of antimicrobials in slaughter animals was initiated in the late 1970s. In line with Directive 93/23, national legislation prescribes that pig producers are not allowed to administer prohibited substances to animals and 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 that are free of residues and prohibited substances are accepted for slaughter. The private program carried out by the abattoir is in place to fulfil these requirements. Additionally,

the private program verifies compliance with quality requirements laid down by trade partners (i.e. the export market). The private program is operative since 2006.

Surveillance objective and expected outcome – The objective is to show to the EU that the legislation regarding MRL in pig meat is complied with through prevalence estimation. Documenting a low prevalence of residues of antimicrobial substances to facilitate trade is an additional expected outcome of the private program.

Surveillance components - There is an official and a private component, each covering finishers, sows and boars.

Handling of suspect and positives – The official program is run as a monitoring program as such that test-positive carcasses are released into the food chain, unless they are, prior to sampling, considered suspect based on visual inspection (i.e. suspicion that the animal is ill or being treated with antibiotics, such as marks of injectables or other lesions, or information provided on the food chain information form). Confirmed positive samples are followed by legal prosecution of the pig producer. Contrary, the private program is run as a surveillance program as such that carcasses that test positive in the screening are released into the food chain, but the next delivery from the farm of origin is blocked and a report on the cause of the residues and potential corrective actions is made.

Actions taken to prevent presence of residues of antimicrobials in pig meat – The quality assurance in place requires pig producers to focus on compliance with withdrawal times. These are supported by legal requirements.

Testing protocol – The diagnostic method used is microbial screening and post-screening, implying re-testing of samples that are found positive in the initial screening. For both screening and post-screening, the Nouw's Antibiotic Test is used (Pikkemaat et al., 2009). This is followed by chemical confirmation using HPLC LC-MS/MS of positive samples, whereby the exact substance and quantitative amount are established.

Renal pelvis fluid is used as sample matrix for screening, whereas meat and/or kidney fluid for post-screening and meat for chemical confirmation.

Study design and sampling strategy – The sampling in the official program is undertaken at random. In the private program, sampling is risk-based for finishing pigs and at random for the sows and boars. For the risk-based sampling, all samples are taken from finisher herds that are defined as 'high-risk' (based on a known history of chronic pleuritis and pneumonia).

3.1.3. The Swiss program

The Swiss national program consists of an official program only.

Surveillance objective and expected outcome – Apart from controlling compliance with MRLs as required by the EU legislation, the objective of the Swiss program is to estimate and monitor the prevalence of antimicrobial residues in pig meat.

Number of surveillance components – The surveillance program is organized only with a public frame. There is no private program regarding antimicrobial residues in pig meat.

Handling of suspect and positives – Sampling does not imply to store a carcass until the test result is available. In case of a positive result, actions are taken directly to the farmer: outbreak investigation, payment of the analyses, and possible restrictions are put on the premises, if considered needed by the authorities.

Actions taken to prevent presence of residues of antimicrobials in pig meat – There is a growing concern among Swiss farmers and veterinarians regarding antimicrobials and the way they are used. In response, campaigns regarding prudent use are becoming more prevalent (Schaller, Caspari, & Kümmerlen, 2015). Such actions are not targeting specifically the residues but raise awareness in the supply chains. Moreover, the two main food distributors might refuse to buy meat from a non-compliant farmer, increasing the incentive to comply with the EU standards represented by official legislation and private standards.

Testing protocol – At the cantonal level and depending upon the kind of antimicrobial, different diagnostic methods are used such as four-plate, liquid chromatography/Time-Of-Flight (LC/TOF) and ultra-high performance liquid chromatography coupled high resolution mass spectrometry (UPLC-HRMS) and HPLC LC-MS/MS. Kits for testing as well as for national proficiency testing are sent once a year from the national reference laboratory to the cantonal laboratories involved in residue testing.

Liver, meat, and kidneys are used as sample matrix.

Study design and sampling strategy - As the number of slaughtered pigs per year is relatively small (N = 2.7 millions of pigs slaughtered per year), the total amount of samples tested for all kinds of residues including legal antimicrobials in accordance with EU Directive 96/23, remains small (0.05% corresponding to 1370 samples). Samples are distributed each year by the national coordinator in collaboration with the national laboratories. The distribution reflects the production size in each canton and the seasonality of antimicrobial use. The sampling strategy is following EU Directive 96/23 which specifies the sampling frequency and hereby the number of samples. Operators are then asked to target, if possible, susceptible animals based on their experience as well as on sex, age, species and production system as recommended in the EU legislation (Swiss Confederation, 2016).

3.2. SWOT analysis of the programs

The SWOT analyses are presented by country, so Table 2 contains results for Denmark, Table 3 results for the Netherlands, and Table 4 results for Switzerland.

4. Discussion

The aim of the study was not to rank the quality of the programs but to make a comparison aiming at understanding how the countries' individual needs were expressed in the programs. Although we only compared the programs in three European countries, we show that there is a substantial variation in how the programs are set up and run. Moreover, based on the analysis we can argue where it may make sense to harmonize or allow for flexibility. Still, there may be issues which we have not fully covered. Therefore, the recommendations should be interpreted as an input for the discussion about the future legislation regarding residue monitoring.

In the following paragraphs, the balance between flexibility and harmonization is discussed for each key attribute of the residue program in the three countries based on the evaluation of the monitoring programs as well as the results of the SWOT analysis. We have focused on residues of antimicrobial origin in pig meat, but the considerations are applicable for monitoring of all residues in all livestock species.

4.1. Surveillance objective and expected outcome

Although the evaluation revealed that the surveillance objective of the residue programs in the three countries was the same (to show to the EU that the legislation is complied with through prevalence estimation), the expected outcome differed. Some of the variation may be explained by differences in the risk perception regarding the human health impact of residues in meat. Apart from this, the trade in pig meat seems to act as a major driver for the dimensioning of the monitoring programs for residues of antimicrobial origin. For countries exporting pig meat to markets outside the EU – such as Denmark and the Netherlands - there is a

Table 2
SWOT Analysis of the Danish surveillance-and-control program for residues of antimicrobial origin in pig meat – covering the official and the private program - based on a description made by the RISKSUR Tool, 2017

Internal situation	
Strengths	Weaknesses
1. Use of HPLC LC-MS/MS makes it possible to analyse for presence of several substances at the same time – including some illegal substances 2. Accredited labs are a guarantee for high quality and functionality 3. Collaboration between public and private program - regarding use of the same laboratory method (HPLC LC-MS/MS) and matrix (meat) – implies a high repeatability 4. Several incentives are in place at the pre-harvest level focusing on prevention; i) Instruction regarding correct injection technique including shaking of bottle and choice of injection site ii) Clear marking of treated animals e.g. using rubber band around the leg iii) Recording of all treatments iv) Choice of "best" substances v) Almost all pig producers are member of the quality assurance scheme called Danish Product Standard 5. Industry penalty system in place (finding > MRL)	1. The programs require training of personnel at different levels 2. High total cost related to the programs due to the large number of samples taken 3. The policy of interpreting the program as surveillance - and not as monitoring - is costly, because it requires that actions are taken upon knowledge: i) The abattoir is withholding carcasses, which form part of testing, until a negative result becomes available – and the green and red offal from these animals are condemned resulting in extra costs ii) Extensive trace-back is undertaken, if animals have been sent to slaughter prior to the end of the withdrawal period. This occurs when the farmer calls in too late, and the animals are slaughtered, the carcasses cut and mixed with other carcasses
External situation	
Opportunities	Threats
1. Availability of a large number of sample results (with negative results) gives high confidence among trade partners 2. HPLC LC-MS/MS provides negative/positive lab results within 24 h with minimal impact on the production process (cutting and deboning). Further, This enables effective herd visits within a week, conducted to identify reasons for presence of residues, and required before farmer can deliver animals for slaughter again 3. If MRL values are lower on a specific export market, actions can be taken; i) Prolongation of withdrawal times ii) Application of lower MRL values for certain substances for carcasses/meat destined to these markets	1. Risk-based sampling among finishing pigs results in an apparent higher prevalence of residues compared to random sampling - if results are communicated for finishing pigs as such 2. Targeted sampling giving higher weight to sows than to finishing pigs results in an apparent higher prevalence of residues compared to sampling with equal sampling frequency - if results are communicated for swine as such

Table 3
SWOT Analysis of the Dutch surveillance-and-control program for residues of antimicrobial origin in pig meat – covering the official and the private program - based on a description made by the RISKSUR Tool, 2017

Internal situation	
Strengths	Weaknesses
1. Risk-based sampling increases cost-effectiveness of the program 2. Private program enables farmers to fulfill (national) legal requirements with regard to self-control on residues of veterinary medicinal products. 3. Test procedures with a short interval between sampling and test result enable effective follow-up of non-compliant results (via herd visits).	4. Risk-based sampling requires a transparent, standardized approach in which selection criteria are objective and clear to the staff performing the sampling. 5. Data regarding results of the monitoring activities should be easy accessible (and distinguishable between random and risk-based sampling) in order to evaluate the efficacy of the sampling protocol. 6. Herd visits are based on microbial screening, which leads to a number of unnecessary visits (when chemical confirmation does not indicate violation of the MRL). This decreases the cost-effectiveness of the program but contributes to the prevention of new cases.
External situation	
Opportunities	Threats
4. A transparent surveillance program on antimicrobial residues including feedback into the food chain contributes to growing awareness and interest of farmers regarding antimicrobial residues. 5. Exchange of information on programs and outcomes between private and public sector to consider overlap and gaps. 6. Frequent evaluation of the outcomes of the program enables optimization of resource allocation.	1. Effective risk-based sampling may suggest an apparent higher prevalence of residues compared to random sampling if results are not communicated appropriately. 2. For third countries (trade partners) residue programs are not easy to handle with risk of trade blockades

perceived need for demonstrating a low prevalence of residues of legal substances and absence of illegal substances on certain export markets. In this context, follow-up of non-compliant results and preventive and corrective measures are important to show to trade partners to avoid negative reactions and call-back of meat. This contrasts with countries such as Switzerland, which trades pig meat on the EU market but does not have an export out of the EU. Here, the need for documentation is less profound and it suffices to fulfil the basic EU legislation.

In the current EU Directive, the overall objective of monitoring of veterinary medicinal drugs – including antimicrobials - is to verify compliance with the Maximum Residue Limits (MRL). It has been suggested that the overall objective could be changed to provide data for an assessment of the dietary exposure of consumers to veterinary medicinal products (The EU Commission, 2004). However, the public health risk related to antimicrobial residues may be considered as very low, because the prevalence of residues in pig meat is low and, even more important, human cases

Table 4
SWOT Analysis of the official Swiss program for residues of antimicrobial origin in pig meat - based on a description made by the RISKSUR Tool, 2017

Internal situation	
Strengths	Weaknesses
1. Use of HPLC LC-MS/MS makes it possible to analyse for presence of several substances at the same time – including illegal substances (the latter is only part of the official program) 2. No immediate impact on the products: the program is organized as a monitoring system. The result is not a releasing factor. 3. Strong organization of the different official laboratories involved in the project i) Distribution of the samples between all the different laboratories ii) Sample kits sent to the abattoirs and place of sampling to ensure the quality of sampling and transfer. 4. Switzerland has a small production and almost no export: flexibility of the system, costs relatively low, coordination with a limited number of people.	1. Non-harmonized use of diagnostic methods for screening and verification between cantons 2. Low number of samples per year: the EU Directive asks for a small percentage of samples regarding the whole production. The significance of the output can be discussed. 3. The training of official veterinarians and chemists take place only once in their carrier. It can affect their interest, motivation and work for this program. 4. Data base of the program: the data collection and data transfer has not been systematised leading to loss of data or difficulties to access them after the annual report.
External situation	
Opportunities	Threats
1. General growing awareness and interest of farmers regarding AM residues: development of programs for a better use of AM. 2. Federal and cantonal developed initiatives about drug residues in other products (e.g. milk) according to the interest of the concerned government.	1. Difficulties may occur in case of export depending on the requests and conditions of the importer.

are not reported. This implies that antimicrobial residues in pig meat may be interpreted more as a public health issue than a real food safety issue – as suggested by Alban et al. (2014). To prevent presence of residues in meat, it may be more appropriate to continue having verification of compliance with legislation as the official overall objective instead of changing to assessment of dietary exposure. The latter objective may need a high number of samples, which may require more economic resources. Instead, it may be suggested to using test results from positive samples with concentrations of residues below MRL. However, the biological methods used for screening in some countries may have a low sensitivity for concentrations of residues below the MRL. This may imply that such data may not be comparable with data collected using direct chemical verification (e.g. HPLC LC-MS/MS), also because a central recording of the kinds of biological tests used in the different countries is currently not available. Instead, test results covering a number of years may be used for an assessment of the human exposure.

4.2. Surveillance components

Denmark had four surveillance components, the Netherlands two, and Switzerland one. According to Article 9 in the EU Residue Directive 96/23, a minimum of two components – an official and a private - are recommended without a specification of the size of the private component. A private component will put responsibility on the Food Business Operator, in this case the abattoir and the pig producers, and this may act as an incentive to reduce the prevalence of residues in meat further. Therefore, a minimum of two components should continue to be recommended in the EU legislation.

However, if the livestock population is small and scattered with a low number of animals slaughtered in a high number of abattoirs, it may not be feasible to have a private component. Moreover, if only few samples are found positive in the official program annually, and human cases are found only seldom (and if found the symptoms are mild in accordance with Baptista et al., 2010), then the incentive to spend extra resources may not be present. This challenge may be solved by specifying in the coming legislation that small abattoirs are exempted from taking samples routinely as a part of a private program.

4.3. Handling of suspect cases

An elevated within-herd prevalence of chronic pleuritis, measured using *post-mortem* data, is used as an indicator of high-risk finisher pig herds in the private programs in Denmark and the Netherlands. The increased probability of finding residues in carcasses from such herds can probably be explained as a higher need for use of injectable antimicrobials for treatment of the respiratory infections present compared to other herds (Alban et al., 2014).

When pigs are to be injected with antimicrobials, it is recommended to do this in the neck due to the low price of the meat for the forepart of pigs. Marks of injection may be an indicator for abscess formation – and abscesses are known for being associated with a slower clearing of the antimicrobial from the area implying that the concentrations of residues may be higher than expected in this area after the end of the withdrawal period. This was e.g. found by Johansen. (1997) who noted that the risk was higher when large volumes of oil-based ampicillin was used compared to water-based penicillin. However, in the daily life at an abattoir, injection marks may be difficult to detect during lairage or at *ante-mortem* inspection, because they are not necessarily visible macroscopically from the outside of the body. During post mortem, such abscesses may not be detected, unless located in the middle of the neck, due to the splitting of the carcass. This implies that it may be difficult to use injection marks as a feasible indicator for suspect animals. In fact, marks of injections is not used routinely by the largest Danish abattoir company despite that this is stated in the Danish industry code as a reason for considering an animal as suspect for residues of antimicrobials (S.W Christensen, Personal comment 2017).

4.4. Handling of positive cases

As stated earlier, there may be a slight difference between the three countries regarding the perception of the risk to public health represented by presence of residues of antimicrobial origin in pig meat. In Denmark, the program is run as surveillance and not as monitoring, because actions taken in case of a positive sample are comprehensive and consist of withholding carcasses until a negative test result is available, trace back and eliminating positive carcasses from the food chain – in line with the definition of surveillance and monitoring suggested by Hoinville et al. (2013). In the

Netherlands, studies have shown a negligible human health impact related to occasional finding of very low levels of residues in meat (Berends et al., 2001). Therefore, actions in case of finding residues are targeted towards prevention; implying that the herd is contacted to identify reasons for presence of residues. In Switzerland, consumer concern is growing regarding use of antimicrobials and associated residues in food, and therefore initiatives have been made by farmers to reduce the use of antimicrobials and the presence of residues in meat. When designing the monitoring for residues of antimicrobial origin in meat, the Swiss national coordinators have had focus on compliance with EU instructions regarding sampling, while accepting that the actions taken after a positive sample target only the farmer and not the carcass.

Directive 96/23 does not contain a clear indication of whether carcasses for testing should be detained until a negative test result is made available. This facilitates individual country-specific interpretation of the need for acting upon findings of residues above the MRL in the screening as described above. It would be most helpful, if the coming EU Directive about residues will be more specific about the need for detaining and subsequent handling of positive carcasses. It seems disproportionate to destroy carcasses with concentrations of legally used antimicrobials above MRL, because the risk to public health is very low (Baptista et al., 2010; Berends et al., 2001). Moreover, the surveillance system sensitivity of the programs is very low – For the Danish program it is around 0.1% (Alban et al., 2016) - meaning that the clear majority of the positive carcasses are not detected. Therefore, to avoid food waste it may be suggested to interpret the results from screening at the abattoir not as a food safety criterion but as an indication of the level of the farmers' compliance with good farming practices. Actions may consist of a detailed follow-up visit of the herd of origin to elucidate reason for presence of the residues. Furthermore, animals delivered for slaughter in the subsequent period should be tested and the costs put on the producer. Such systems are currently in place in all three countries selected for this study. Additionally, the individual Food Business Operator may choose to apply extra guarantees and withhold such carcasses until negative testing results are made available e.g. to fulfil trade partners' requirements – the latter is currently done in Denmark and the Netherlands.

4.5. Preventive activities

One may assume that the pre-harvest initiatives to prevent presence of residues in in millions of slaughter animals have a larger impact than the monitoring for residues in some thousands meat samples. Moreover, it might be hypothesized that swine producers may be more inclined to comply with the legislation, if they are informed about how and why they should comply and what will happen if they are not complying. This view is reflected in the many different activities in place to prevent residues from being present in place in all three countries. Control campaigns are undertaken by the veterinary authorities involving visits to pig producers during which compliance with the legislation in place is checked. Moreover, private standards are in place for pig producers committing them to apply e.g. a longer withdrawal period for tetracyclines and requiring correct injection technique as well as proper marking and routinely recording of treated animals (Knowledge center for Swine Production - SEGES, 2016; IKB-Varken, 2017). These standards are acting on top of the legislation, and they are voluntary by nature. However, many abattoir companies require their farmers to use the standards; in Denmark 95% of the pig producers conform to the standard developed for pig production. Moreover, pig producers in Denmark, the Netherlands and Switzerland are informed at regular intervals about the consequences for export/trade related to presence of residues in meat and that they will be fined if concentrations above MRL are found.

4.6. Testing protocol

Different diagnostic tests are in place in the three countries. In Denmark, direct use of HPLC LC-LC/MS for screening is in place both in the official and the private program. In the Netherlands, biological methods are used followed by a chemical verification of suspect samples using HPLC LC-LC/MS. In Switzerland, different chemical methods are in place for direct verification. As stated further up, the biological methods hold an acceptable sensitivity for samples with concentration of antimicrobials close to the MRL level (Pikkemaat et al., 2009). This implies that any diagnostic method can be accepted conditioned it can be documented that it is conforming to the requirements in EU Decision 657/2002 concerning the performance of analytical methods (The EU Commission, 2002). According to EU Directive 96/23, the EU Reference laboratory is addressing issues regarding diagnostic test performance on regular meetings with the national reference laboratories.

The testing matrix also varies between the three countries; Denmark uses meat, the Netherlands renal pelvis fluid, and in Switzerland liver is used. Antimicrobials absorbed into the body have a higher concentration in the kidney than in the meat. Therefore, kidney or renal pelvis fluid has been used as the testing matrix to account for the lower sensitivity of the biological methods, which used to be the only feasible way of testing for residues. However, most consumers eat meat and not kidney, and therefore it may be argued that it is more appropriate to test meat – and that can be done, if for instance HPLC LC-LC/MS or other chemical methods are used as diagnostic method, because these methods have a very high sensitivity. The difference in concentrations of antimicrobials in meat and other tissues such as kidney is – at least in theory - already reflected in the MRL, which is higher in kidneys than in meat. It may therefore seem unnecessary to set official requirements for the testing matrix and instead leave it to the country or abattoir to decide whether and how to test meat, kidney or liver.

4.7. Study design

The surveillance objective is to show compliance with EU legislation through estimation of the prevalence for residues. Some degree of harmonization would be useful e.g. with a minimum sampling frequency as in the current legislation. This will allow for a comparison of the prevalence of residues in meat, which may be expected to act as an incentive to reduce the prevalence further.

However, the sample size in the official programs is low in most countries implying that the precision becomes low too. The current requirement for the official sampling is 0.01–0.02%. Hence, 3000 samples are to be taken in a population (N) of 15–30 M slaughter pigs. Based upon slaughtering figures for 2013, it may be concluded that a sufficient number is taken as part of the official sampling in Germany (N = 58.6 M), Spain (N = 41.4 M), France (N = 23.7 M), Poland (N = 19.1), Denmark (N = 19.1 M), and the Netherlands (N = 14.0 M), whereas a lower number of samples are taken in the other EU Member States (Eurostats, 2014). This implies a lower precision (=more uncertainty) on the prevalence estimates in the latter countries which may be compensated by evaluating the results from monitoring taken over multiple years.

If the objective were to detect at least one positive sample, then the sample size becomes immense for countries, where the prevalence of residues is low. This was e.g. shown by Baptista et al. (2012) who calculated that random testing of 20,000 Danish finishing pigs would only result in 72% probability of detecting at least one positive sample, because the prevalence of residues in meat in

Danish finishing pigs is only around 0.01%. For sows and boars, testing of 2000 animals would suffice to detect at least one positive, because the prevalence in Danish sows and boars is around 20 times higher than in finishing pigs (Baptista et al., 2012).

Alternatively, a fixed sample size may be added to the regulation, which can guarantee that if residues are present at a given design prevalence or above, then they will be detected with 95% confidence. For example, if 3000 samples are tested and found negative while assuming that a test with 100% sensitivity and specificity was used, then the maximum prevalence in the population is 0.1%. If a positive sample is found, then the statistical assumptions behind the calculations are violated. This implies that the formula regarding prevalence estimation should be used. If 3000 samples are taken, and the prevalence is assumed to be 0.1%, then a precision of 0.12% can be expected, when estimating the prevalence with a 95% confidence level (WinEpiscope). Irrespective of the way of calculating, the conclusion is the same: the prevalence is very low.

In Directive 96/23, the testing protocol for residues is set at a fixed proportion. For legal antimicrobials – which are used and therefore occasionally found - this may seem adequate. However, for forbidden substances some degree of flexibility – using the *bonus-malus* principle - could be considered as more cost-effective. This could e.g. consist of a minimum monitoring for substances which have not been found in monitoring for several years as well as a higher/increasing sampling intensity for substances, which have been found. This reflects that it is not the monitoring program itself, which prevents the presence of residues in meat. If there have been no findings of an illegal substance for many years, then the incentive for using that substance is not present, and resources for sampling do not need to be invested. This view has also been expressed among several EU Member states (The EU Commission, 2004). In Denmark, that would mean a very limited sampling for forbidden substances; only one sample from a finishing pig has tested positive within the last 20 years and that was for diethylstilboestrol. No source was found and there was no apparent incentive for the use, therefore, the finding was classified as an artefact (van Maarschalkerweerd, Olsen, Dresling, & Alban, 2016). Still, the recent finding of the insecticide fipronil in eggs and egg products in the EU in mid-2017 points to the continued challenge of how to be prepared for detection of presence of substances that are not meant to be present in a food item (The German Federal Institute for Risk Assessment, 2017b). Here, rapid alerts are an effective instrument to fast movement of information, whereas traceability systems are required to assist mitigating the identified risk.

4.8. Sampling strategy

One-stage sampling at the abattoir (implying direct selection of which pigs to sample) was the most commonly used sampling approach; two-stage sampling at the abattoir (implying that first herds are divided into high-risk and low-risk, and then animals within these strata are selected) was only in place for the private programs for finishing pigs in Denmark and the Netherlands.

Random sampling is not very efficient for detection of rare events such as presence of residues in meat. Instead, risk-based sampling – previously by some called targeted sampling - can be recommended through increased sampling in high-risk population strata as suggested by Stärk et al. (2006) and Hadorn and Stärk (2006). This is in line with EU Decision 98/179, which specifies that sampling for residues should be risk-based considering sex, age, species and farming system (The EU Commission, 1998). This is seen in the Danish programs, where the testing frequency is 20 times higher for sows and boars compared to finisher pigs. This way of setting up the program is reflecting Danish data from monitoring which showed that sows and boars have a 20 times higher probability of harbouring residues than finishing pigs (Baptista et al., 2012). However, if the overall objective is to demonstrate a very low prevalence of residues in meat from finishing pigs to trade partners, then there is a limited value of additional testing in sows and boars. Here, use of an indicator associated with high risk within a sub-population is needed. This approach is used in the Danish and Dutch private programs for finishing pigs, where high-risk herds are herds with a very high prevalence of chronic pleuritis compared to the national mean.

To ensure cost-effectiveness, risk-based sampling should be recommended in the coming legislation. However, to become meaningful, identification of risk factors or indicators should preferably be evidence-based. This implies collection of a substantial number of up-to-date within-country test results combined with information about presumed risk factors or indicators, whereby the relative risk of such factors can be assessed at least with some precision. Such analyses should ideally be published to act as inspiration for others and to increase the confidence in risk-based testing. These requirements should, however, not limit the possibility to try out different approaches. Hence, flexibility should be allowed e.g. by letting the Competent Authority commission a risk assessment ascertaining the effect of potential indicators or to evaluate a similar risk assessment undertaken by the industry. The latter approach is in place in Denmark and the Netherlands.

The largest disadvantage related to risk-based sampling is that the true prevalence in the population cannot be estimated – unless the results are compared to a randomly sampled part of the population. In Denmark, the prevalence of chronic pleuritis (and other chronic meat inspection lesions) in herds where residues were found during a period of 1.5 years was compared to the abattoir's mean prevalence. Hereby a RR of 2 was estimated for chronic pleuritis (Alban et al., 2014). This is close to the RR of 3.2 for chronic pleuritis found by Jelsma, Lesuis, and Ronteltap (2006) in similar Dutch data.

Despite that testing in Denmark and the Netherlands involves thousands of samples, the surveillance system sensitivity is low. This implies that most of the positive cases are overlooked (Alban et al., 2016). Still, the programs are considered effective, because they act as an incentive for the pig producers to prevent sending animals with residues of antimicrobials for slaughter.

4.9. Data generation/analysis and dissemination of results

More harmonization and transparency in reporting would be beneficial. EFSA has recently published a guideline for reporting data on residues of veterinary medicinal products (EFSA, 2015). This report focuses on relevant laboratory issues such as types of matrix and diagnostics. However, it does not include the sampling approach. To avoid discouraging use of risk-based sampling (which is aimed a sampling in sub-populations with higher risk), data should be divided according to whether the monitoring is risk-based or random. In the Danish case, this would imply that data should be divided according to the four surveillance components. If this is not done, then any comparisons may be meaningless.

4.10. Evaluation of usefulness of the RISKSUR tool and the SWOT analyses

The application of the RISKSUR design tool for monitoring of antimicrobial residues in pigs showed that the tool is generally well applicable. Nevertheless, some revision of terminology is suggested to improve its applicability to non-infectious hazards. One of the first surveillance key attributes covered by the tool is the

surveillance objective. Options to choose include case finding, estimate prevalence, freedom from disease and early detection.

However, the objective of monitoring of antimicrobial residues due to veterinary medicinal products, as described by EU Directive 96/23, is "controlling the compliance with MRLs for residues of veterinary medicinal products". Prevalence estimation is perhaps most in agreement with the text in the Directive, although the required sample sizes for the official monitoring as laid down in the Directive are not sufficient for accurate prevalence estimation in most EU Member States as highlighted in Section 4.7.

Currently the RISKSUR design tool only involves the design and description of "monitoring" and "surveillance" components. The addition of the objective "verifying compliance" would be most relevant to add, but also details of inspection activities and enforcement mechanisms – as suggested by Flewwelling (1995).

The SWOT analyses were made for each country using input from a stakeholder group consisting of people involved in monitoring of antimicrobial residues in that country, and each analysis was led by a co-author from the specific country. The weakness related to this approach was the lack of structure, which made it difficult to fully compare the results. On the other hand, the approach made it possible for the stakeholder groups to come forward with their views and experience of what was considered most important in each their situation.

To avoid trade disruptions, EU has developed a set of guidelines for non-EU countries intending to export food, including meat, to the EU. The focus of the guideline is all kinds of residues including legal and illegal veterinary medicinals. According to these guidelines, the exporting country should set up a plan in which it is described how the following key requirements are fulfilled: 1) the residue monitoring plan must be centrally coordinated, 2) the relevant national legislation must be described, and 3) the testing frequencies should be like the ones prescribed in EU Directive 96/23. Furthermore, the plan must describe details on measures to be taken in the event of a non-compliant (positive) result as well as a list of approved laboratories for residue testing and their accreditation status. The plan should be sent to the EU Commission, which then evaluates whether the documentation provided can offer guarantees at least equivalent to those in EU legislation (DG Health and Food Safety, 2017c). The guidelines are very useful as a start to set up a monitoring program. However, the guidelines do not go into the same level of details as we have been able to do using the RISKSUR tool, where focus is broader and among others includes preventive actions, considerations about how to go risk-based and ways of reporting.

5. Conclusion

The future EU Directive about monitoring for residues of antimicrobial origin should focus on the objective of residue monitoring: to demonstrate compliance with legislation regarding MRL for legal antimicrobials and absence of use of prohibited antimicrobials. Moreover, standards for monitoring should be set to ensure a basic level of monitoring that can enable a comparison of results, acting as an incentive to reduce the prevalence of residues. If the annual number of samples collected in a Member States is too low to produce precise prevalence estimate, more years of data may be used. Official handling of positive carcasses on the abattoir should also be harmonized e.g. by interpreting screening results as an indication of the level of the farmers' compliance with good farming practices and not a food safety hygiene criterion implying no detaining of carcasses to be tested and no withdrawal of positive carcasses, but follow-up visits in the herd of origin and testing of animals delivered for slaughter in a subsequent period. Risk-based sampling should be encouraged as a way of ensuring cost-effectiveness. Results from risk-based and random sampling should be reported separately in order not to discourage risk-based sampling. Harmonization is not necessary for number of surveillance components (but a private component is recommended), preventive activities, diagnostic method (HPLC LC-LC/MS versus biological methods), and way of sampling (meat or kidney/risk-based or random).

Overall speaking, the RISKSUR design tool proved to be adequate to describe and compare the different monitoring programs for residues of antimicrobials.

Declaration of interest

The authors declare that they have no competing interests.

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