DIGITAL TRANSFORMATION OF ANIMAL HEALTH DATA: PROCEEDINGS OF THE AHEAD 2017 WORKSHOP

EDITED BY: Flavie Vial, András Székács and Sinead Quealy

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DIGITAL TRANSFORMATION OF ANIMAL HEALTH DATA: PROCEEDINGS OF THE AHEAD 2017 WORKSHOP

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The industry-wide move towards an increased digitisation of animal health is making real-time monitoring of drug usage in livestock possible today.
Image copyright: VirtualVet

The Organisation for Economic Co-operation and Development (OECD)'s Co-operative Research Programme on Biological Resource Management for Sustainable Agricultural Systems sponsored the AHEAD 2017 workshop, bringing together experts from the farming and pharmaceutical industries, information and communications technology, policy, research (and more) to create a roadmap to the digital transformation of animal health surveillance.

In many countries, policy supports the reduction of antibiotic use and a growing focus in the veterinary practice is to move away from blanket dosage of antibiotics, for example for mastitis. Significant and speedy improvements can take

place, but only with coordinated actions supported by the entire value chain. Reducing the use of antibiotics is of massive societal importance, but changing on farm or veterinary methods requires thought and a user-centred approach. The most glaring and addressable challenge is the absence of near real-time data and information.

AHEAD 2017 explored how governments globally can benefit from increased digitisation in animal health. For effective monitoring, it is important to first understand the relevant tasks of each stakeholder in the food value chain. In these proceedings we openly discuss and define these tasks, identify existing challenges to completion of these tasks, and suggest the business opportunities overcoming these challenges can create. Through this publication, it is our intention to encourage open discussion, design and co-creation of an improved digital approach to animal health and drug usage in agriculture.

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Editorial: Digital Transformation of Animal Health Data: Proceedings of the AHEAD 2017 Workshop

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Editorial on the Research Topic

Digital Transformation of Animal Health Data: Proceedings of the AHEAD 2017 Workshop

Experts from government, farming, information and communications technology, policy and research convened on March 1st and 2nd 2017 in Exeter (UK) to create a roadmap to the digital transformation of animal health surveillance. The workshop, supported by the Organisation for Economic Co-operation and Development (OECD)'s Co-operative Research Programme on Biological Resource Management for Sustainable Agricultural Systems, was attended by representatives from 10 OECD countries (Australia, Belgium, Estonia, Hungary, Republic of Ireland, the Netherlands, Sweden, Switzerland, the United Kingdom and the United States of America)

Prof Toby Mottram's opening words to the workshop, "We need a better picture of the creature we are trying to create", resonated with all participants. In an attempt to sketch that picture, the structure of the workshop and of this editorial is very much aligned with the magic triangle for business models (1): Why? What? and How?

In this research topic, 21 authors contributed 9 articles (3 perspective pieces, 5 opinion papers and 1 review) arguing the paramount importance of collecting digital animal health data to strengthen our understanding of emerging issues including antimicrobial resistance; identifying the frameworks and tools required to support this digital revolution and proposing new societal and business models to profoundly change the way we all think about digital data.

THE "WHY" OF ANIMAL HEALTH DATA DIGITISATION

In the EU, policy supports the reduction of antibiotic use, through the March 2016 new Animal Health Law (Regulation 2016/429), and a growing focus in the veterinary practice is to move away from blanket dosage of antibiotics, for example for mastitis. Significant and speedy improvements can take place, but only with coordinated actions supported by the entire value chain. Reducing the use of antibiotics is of massive societal importance, but changing on farm or veterinary methods requires thought and a user-centred approach. The most glaring and addressable challenge is the absence of near real-time data and information. AHEAD 2017 explored, in the context on EU Animal Health Law, how governments globally can benefit from increased digitisation in animal health.

Antimicrobial usage and resistance research data needs are explored in Magouras et al.; Pinto Ferreira. Many fairly simple questions still remain without clear answers: what quantity of antimicrobial drugs are used in veterinary medicine for different species? What are the social factors contributing to antimicrobial usage in the farming industry? How can we measure the association between antimicrobial usage and resistance? What environmental factors or contaminants accelerate antimicrobial resistance,

what is the flow and fate of antimicrobial drugs and resistance into the environment and wildlife? In relation to the later, the review by Klátyik et al. brings to light the extent of the problem of residues of the active ingredients and adjuvants of veterinary drugs entering the food and the feed chains. The digital collection of data on veterinary drugs from production at pharmaceutical plants to their prescription by veterinarians and ultimately their usage on farm would provide elements of answers to all these questions. A strong call to action from industry stakeholders to see the wider value in early and digital data collection is made by Barrett.

THE "WHAT" OF ANIMAL HEALTH DATA DIGITISATION

The sequence of processes required for evidence-based animal health decisions are delimited (Vial and Tedder) where the challenges to near real-time farm data analysis and interpretation are explored in more depth. These challenges include, but are not limited to, the weak adoption of standards and control vocabularies (for data interoperability), the need for data privacy and security, the need for modelling methods capable of handling high dimensionality and large sample size, and the need for context during output interpretation. Open global standards for use in the recording, storing, and sharing of data by the food and other industry sectors worldwide do exist and are presented (Bracken). If employed more widely along the animal production chain, these standards could make data capture at the point of treatment of the animal(s) and digital drug records a reality. Information technology systems accessible to decision makers working in the livestock industry have emerged, and Alawneh et al. presents one such system developed and used in New Zealand. Timely access and appropriate analysis of dairy herd productivity data is used to guide the allocation of resources to the most promising herd health interventions.

THE "HOW" OF ANIMAL HEALTH DATA DIGITISATION

Kärner explains how Estonian farmers, as all Estonian citizens, benefit from the usage of e-services. Estonian political and technical leadership laid the foundation for e-Estonia in the early 2000s on the principles of (1) decentralisation, (2) interconnectivity, (3) open platform and (4) open-ended process. Some of these principles are echoed in Lynch and Quealy's participatory market model for the animal health industry. The animal health value chain has traditionally been a closed captive prescriptive market model built on transactional relationships and resulting in knowledge being siloed and in inefficient resource utilisation. Lynch and Quealy describe data ownership as "the most frequent roadblock" encountered when trying to engage with stakeholders in discussions around improved data capture and sharing. Today, this value chain is rapidly evolving with many new participants (e.g., feed and pharmaceutical companies) and the increasing capabilities of smart, connected products redefining the food-production industry. This context provides an opportunity to overcome these data tensions through the adoption of new business models to meet the needs of farmers, researchers, policy makers, and consumers.

This research topic draws attention to the fact that the digital transformation of animal health will require the involvement of stakeholders across several sectors and industries. All contributions make clear that a considerable number of frameworks, practices and tools already exist which can be extended to the animal health and agri-food industries. Researchers have demonstrated the advantages to implementing these as solutions to acknowledged challenges. While this digital transformation still appears to many as daunting, the advantages of such a transformation in data collection and data exchange would be enormous to all stakeholder groups (producers, consumers, pharmaceutical companies, food safety authorities, etc.) along the entire food chain and the wider scientific community

AUTHOR CONTRIBUTIONS

SQ and FV organised and ran the AHEAD 2017 workshop. FV and AS edited contributions to this research topic. All the authors were involved in writing this editorial and agree to its final version.

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Antimicrobial Usage and -Resistance in Livestock: Where Should We Focus?

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Antimicrobials represent one of humanity's medical revolutions enabling us to treat both human and veterinary bacterial infections. It is, therefore, of utmost importance to preserve their effectiveness. However, during the last decades, the continuing rapid development of antimicrobial resistance (AMR) has emerged as a major global public health concern (1). Resistant bacteria may hamper the treatment of infections resulting in prolonged illness, disability, and death (2).

In veterinary medicine, antimicrobials play a crucial role in the maintenance of animal health, animal welfare, and food-safety (3). However, a not yet quantifiable share of the burden of resistance for public health is attributable to the use of antimicrobials in livestock production (4–6). Farm animals are exposed to considerable quantities of antimicrobials (7) and can act as an important reservoir of AMR genes, which could be transmitted to humans through the food chain, direct animal contact and the environment. Use of antimicrobials in agriculture also includes those defined by the World Health Organization (WHO) as "critically important" for human medicine (8). Resistance against these substances can limit dramatically the treatment options against serious human bacterial diseases. Notorious examples include the vancomycin-resistant enterococci (VRE), the extended-spectrum β-lactamase (ESBL) producing *Enterobacteriaceae* and the recently detected plasmid-mediated colistin resistance (mcr-1 gene) in livestock, food, and humans in China (9–11).

Resistant bacteria can be introduced into the environment through several ways, such as the land application of livestock manure as fertilizer (12). The globally rising aquaculture sector, which is characterized by extensive use of antimicrobials, represents another important source of resistant bacteria that can find their way into the environment (13). Our understanding on the epidemiology of AMR in livestock production is also hampered by the lack of comprehensive antimicrobial usage (AMU) data in the majority of countries. Furthermore, AMR development and spread is driven by human behavior, from the prescription of antimicrobials to infection prevention and control. Understanding these factors is a major step toward fighting against AMR.

The complex epidemiology of AMR emphasizes the need for highly interdisciplinary research approaches, comprising humans, animals, and the wider environment. In line with the WHO global action plan on AMR (14), it is the authors' opinion that research should be prioritized toward (a) understanding the social/behavioral drivers of AMU and AMR, (b) establishing or improving systems to monitor AMU, and (c) encouraging a holistic approach through the One-Health concept when addressing the phenomenon and risk of AMR.

SOCIAL SCIENCES

It is well established that resistance to a new antimicrobial substance begins shortly after its introduction; therefore, development of new antimicrobials should not be viewed as the only solution to combat AMR (15). The emergence and spread of AMR is largely influenced by human behavior, which in turn is shaped by cultural, social, political, and economic factors (16). This is also evident

in the wide variation across the globe in patterns of use and resistance to antimicrobials, which cannot always be explained by differences in the diseases present, in health care infrastructure or farming systems (17, 18). Therefore, social sciences can shed light on the multi-faceted reasons that lead to the application of antimicrobials and the development of AMR. Social sciences are also valuable in identifying the most impactful and feasible interventions to counteract the AMR phenomenon.

In livestock production, veterinarians and farmers play a preponderant role when it comes to AMU and AMR. In many cases, veterinarians decide whether to treat an animal or not with antimicrobials, select the antimicrobial to be used, as well as define the dosage and route of administration. Veterinarians also advise farmers on animal health, biosecurity and production management issues that can strongly influence animal health, AMU, and the transmission of resistant bacteria. Farmers are a source of valuable information on farm management, biosecurity, animal health, and welfare that could be used to identify risk factors (and consequently interventions) associated with AMU in livestock.

Surveys and expert opinions are well-accepted approaches for exploring the behavioral basis of AMU and AMR. These methods could provide informative data on the attitudes, motivation, and knowledge of veterinarians and farmers toward AMU and AMR (19). On the other hand, controlled experimental studies that assess the success of specific interventions are rarely conducted. This research area should be expanded to lay the foundations for the design and implementation of intervention strategies toward the reduction of AMU and AMR.

MONITORING OF AMU

Bacteria can be naturally resistant against specific antimicrobial classes (intrinsic resistance) (20), however in the majority of the times, it is the exposure to antimicrobials that provide the necessary selective pressure for the emergence and spread of resistant bacteria. It should be emphasized that non-antimicrobial agents, namely metals and biocides are also implicated in co-selection of AMR (21). Data collection on AMU is an indispensable step in our attempt to understand and fight AMR. Monitoring of AMU allows the analysis of temporal trends in antimicrobial consumption and can ensure compliance with prudent usage practices, programs, or regulations. Furthermore, monitoring systems can assist in identifying the most efficient interventions for optimizing AMU. In combination with AMR data, quantification of AMU can be useful not only in detecting risk factors for the emergence of resistance, but also in describing temporal associations between AMU and AMR. This would provide evidence on the link between AMU and AMR to researchers, as well as policy and decision makers. In addition, analyzing these data can provide a basis for targeted research and development. The need for standardized usage data of high quality and resolution has been stressed by the European Surveillance of Veterinary Antimicrobial Consumption (ESVAC) (22, 23). The abovementioned benefits of monitoring antimicrobial consumption can be boosted when data on consumption per species are available. However, the

resource-demanding nature of such monitoring systems often combined with political and confidentiality issues explains why only a few countries, such as The Netherlands and Denmark, have nation-wide automated monitoring systems in place (24, 25). Monitoring systems that are based on the collection of farm level data allow for the implementation of benchmarking strategies. These make it possible to rank individuals (farmers or veterinarians) by their level of AMU and to implement measures in order to reduce consumption by the top users. This is an additional benefit, given that benchmarking strategies have been quite successful in reducing AMU in the countries that adopted them. Denmark and The Netherlands are among the countries which experienced a drop in antimicrobial consumption following the implementation of benchmarking systems (26, 27). Alternatives to automated systems include performing randomized field studies or extrapolating species' consumption through sales data stratification (28). Nonetheless, automated collection of prescription/usage data should be preferred as long term goals.

THE ECOLOGY OF AMR AND THE NEED FOR A ONE-HEALTH APPROACH

The complex epidemiology of AMR together with the socio-economical drivers make this topic the quintessential One-Health issue. Transectoral and transdisciplinary approaches are a "must-do" to tackle AMR appropriately. A reduction in AMU was not always followed by a decline in AMR, as demonstrated in the case of VRE (6). Reducing the dissemination and transmission of resistant bacteria within and between animal and human populations is central when aiming to fight AMR. The ability of bacteria to disseminate from one setting to another, sometimes over large geographic distances and among the different populations, makes it difficult to explain with certainty the origin of resistant bacteria strains. Therefore, the reservoirs and the transmission pathways of antimicrobial-resistant bacteria merit further investigation, ideally through a One-Health approach.

Livestock trade creates a complex, heterogeneous, contact network that shapes between-herd transmission of infectious diseases. Direct transmission of resistant bacteria is well documented for livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA). Here, animal trade has been identified to be a major driver of LA-MRSA dissemination (29, 30). For other bacteria, such as *Enterobacteriaceae* and in particular *Escherichia (E.) coli*, fecal shedding represents the main route of dissemination, thus not only host, but also environmental reservoirs may exist which constitute multiple, complex ways of resistance introduction and transmission. So far, experimental studies have demonstrated animal-to-animal transmission of resistant *E. coli* under controlled conditions within confined compartments (31). However, potential factors that drive transmission, such as farm management and the farm environment, have not been studied thoroughly for bacteria such as *E. coli* or *Enterococci*. The practice of land application of livestock slurry and manure represents a major source for introduction of resistant bacteria into the environment (12, 21). Animals can as well excrete resistant bacteria

directly in the environment through their feces while being on pastures (32). *E. coli* spends approximately half of its life cycle in the external environment and, therefore, anything contaminated with these potentially antimicrobial-resistant bacteria may constitute a reservoir for their dissemination (33).

Wild animals are usually not treated with antimicrobials; however, they can carry antimicrobial-resistant bacteria from the farm's surrounding contaminated environments. Wild animal species that acquire resistant bacteria could constitute an additional reservoir of AMR in the environment and could function as vectors (and eventually as amplifiers) for dissemination to other species, including humans (34).

It is, therefore, important to improve our knowledge on how animal contacts and trade (direct transmission), farm management, and the wider farm environment (indirect transmission) drive the dissemination of AMR and to identify potential interventions to counteract this phenomenon. Farm management studies could include all those practices that potentially facilitate spread of resistant bacteria within and between farms and from farms to the environment, such as farm hygiene and biosecurity, animal waste management, structure (and construction material) of holdings as well as animal production intensity.

Holistic, One-Health approaches should always be backed with molecular epidemiological data, which can provide information about links between resistance genes observed in different samples, such as from animals of different origin. Resistance genes should be studied not only in animal samples but also in the wider farm environment, such as farmers, other livestock species, farm pets, wildlife, manure, and water. These ecological data can provide the molecular link to characterize reservoirs of resistant bacteria and could support studies on transmission pathways between animal populations but also from animals to humans and *vice versa*. Source attribution can be of help to shed light on the contribution of AMR originating from livestock to the public health resistance burden. Moreover, it can also be an important piece of evidence when developing targeted interventions against AMR. Genomic data might also provide some additional information on potential evolutionary processes in bacteria during transmission within the studied populations. Furthermore, molecular epidemiology data can shed some light on how much of the resistance reservoir is attributed to the spread of resistant bacteria or *de novo* emergence due to AMU selection pressure in the studied farms.

CONCLUSION AND PROSPECTS

AMR is a complex phenomenon and is driven by biological processes and socio-economical factors. Understanding the attitude and knowledge of farmers and veterinarians toward AMU and AMR is a crucial step for the design of strategies to combat this public health threat. The lack of detailed AMU data impacts our ability to interpret surveillance data on AMR and to design efficient interventions. Therefore, monitoring systems to fill this knowledge gap should be prioritized. Finally, the ecology of AMR should be addressed with a holistic, One-Health approach combining expertise from different disciplines, such as veterinary clinicians, public health scientists, microbiologists, wildlife veterinarians, environmental scientists (ecologists), agricultural/forestry scientists, and epidemiologists.

AUTHOR CONTRIBUTIONS

IM wrote the manuscript. LPC provided valuable expertise on monitoring systems for antimicrobial usage and social sciences. KS provided valuable expertise on the topics of One-Health and social sciences. GS-R provided valuable expertise and feedback in all topics included in this opinion manuscript and assisted IM in the conceptualization of the manuscript. All the authors have read and approved the manuscript.

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Why Antibiotic Use Data in Animals Needs to Be Collected and How This Can Be Facilitated

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Antimicrobial resistance (AMR) is currently recognized as one of the most significant threats to public health worldwide. It is a phenomenon that highlights the interconnectivity between human and animal health since any use of antibiotics in humans can eventually lead to resistance in the microbial populations colonizing animals and *vice versa*. In recent years, our understanding of the relationship between the use of antibiotics and the consequent development of resistance in microbial populations to these (or similar) antibiotics has increased. Having accurate data, ideally in a digital format, on the use of antibiotics are therefore of paramount importance. Current obstacles to having such data include, among others, the lack of consensual and harmonized technical methods and units that represent antimicrobial use (AMU), the insufficient incentives to motivate primary producers to report their use of antibiotics, and the inexistence of user-friendly technologies for the collection of such data, despite the generalized use of Internet and electronic devices. Further development and adoption of the units proposed by the European Surveillance of Veterinary Antimicrobial Consumption will contribute to the long-desired harmonization. Rewarding the animal producers (via tax incentives, for example) that use less antibiotics and the development of an app, to which producers could orally report the used antibiotics are among the solutions that could help to overcome the current challenges. I here also argue that having mandatory electronic veterinary prescriptions and awareness campaings, funded via public–private partnerships, should also be considered as methods that could help for the control of societal problems like AMR.

Keywords: AMR, AMU, incentives, public health, data collection

INTRODUCTION

The discovery, availability, and use of antibiotics (antimicrobials in a broader sense) have had a major positive impact on the development and progress of human medicine in the past decades (1). Similarly, antibiotics have also significantly decreased the morbidity and mortality of animals, therefore revolutionizing animal production (2, 3). However, this "golden age" seems to be coming to an end (4), with an increasing number of reports highlighting alarming levels of antimicrobial resistance (AMR), including resistance to last resort options (5), and very few new classes of antibiotic being commercialized by the pharmaceutical industry (6). Thus, the range of antimicrobials currently available for use, with little risk of resistance affecting treatment, is dwindling.

Antimicrobial resistance is a natural phenomenon (7). As most antibiotics are derived from natural sources, microorganisms have been exposed to them throughout evolution; the development of resistance is therefore a natural survival strategy (8). However, the alarming levels of resistance, reported worldwide in animals (9, 10), humans (11, 12), and the environment (13–15), is generally agreed to be a consequence of the massive use of antibiotics in both humans and animals (5, 16) and is also strongly affected by environmental regulator factors (17, 18). The economic importance of AMR is also substantial (19, 20). Therefore, having accurate and easy to analyze data on antibiotic use is of critical importance, as a step to be able to identify the main specific primary drivers for the downstream development of resistance and tackle them.

THE USE OF DIGITAL DATA ON ANTIBIOTICS UTILIZATION

Having (digital) data on antimicrobial use (AMU) would allow for:

i.   Differentiation of antibiotic use by species treated: at the moment, in the vast majority of countries, it is not yet possible to identify in which species a specific antibiotic has been used. Currently, antibiotics targeting multiple animal species are licensed to be sold with the same commercial name (21). This, in turn, limits the usefulness of sales data as it is therefore not possible to know in which species a specific antibiotic that was sold was used (22). Yet having this information is critical to be able to do source attribution, whereby the ultimate goal is to be able to know, which use, and in which species led to the development of resistance. Once this is possible, risk management options can be implemented;

ii. Identification of good and best practices: being able to identify quantitatively which practices (either at the individual producer level or at the national level) lead to a reduced AMU, while ideally keeping the same productivity in animal rearing (23), is critical. These good practices can then be promoted, through policy change based on a solid evidence base (24);

iii. Identification of a temporal association between AMU and AMR; this is particularly useful when use of a specific product/antibiotic is terminated, either on a voluntary basis (eg. farmers or clinicians) or as a result of a legal ban (25); it is in fact crucial to validate the implementation of such legislative measures, that can also target the use of, for example, heavy metals (like silver, copper, and zinc), that due to co-selection and cross-resistance mechanisms, eventually can also lead to resistance to antibiotics (26). Moreover, there is now an intense debate around how long an antibiotic course should ideally be (10, 27), and these data would contribute to clarifying this critical aspect.

iv. Evaluation of specific policies that, for example, target the reduction of AMU: an example of such a policy would be the "yellow card policy" first implemented in Denmark.

Within the scope of this policy, farmers are alerted when their use of antibiotics is above a set threshold based on what would be expected (28). Evaluation of these policies would then allow for their implementation to be adjusted accordingly (9, 25).

In the past two decades, we have seen the advent and generalized use of computers, cell phones, and a range of other electronic devices, together with the booming of the Internet. This technology provides a route to unprecedent data access. Data related to AMU in livestock production, for example, could be made open access and thus readily available online for all interested stakeholders (such as policy makers, veterinary services, etc.). However, this is, unfortunately, not yet the case.

Considering the usefulness of AMU data, the availability of technology, and the higher educational levels of the younger livestock producers, it seems that at least some of the major requirements for increased availability of digital AMU are available in more economically developed countries. However, at the moment, very few countries actually have automated digital data collection for AMU (29). Therefore, most current analyses on AMU are based on sales data which have significant limitations as described previously, to which it can be added the fact that the sale of an antibiotic does not provide any information about its actual use (i.e. how, when, where, by whom). It is therefore important to analyze the reasons that can potentially explain this gap between what would be expected (having digital AMU data) and the reality (most frequently, the best available data is sales data).

CURRENT OBSTACLES AND LIMITATIONS

A critical initial question is: has the scientific community reached a mature and consensual decision regarding which data should be collected and how these should be recorded? Unfortunately, the answer is "not yet" (30). The harmonization and standardization of units and methods to record AMU have long been a goal and pursuit of the scientific community (31, 32). Yet at the European level, for example, the animal species for which AMU data is currently collected are quite diverse, with some countries collecting information for all species, while others only collecting it just for the major livestock species (such as pigs or cattle). Furthermore, the technical unit used to measure AMU at the European level can be the Animal Daily Dose (ADD), the Defined Daily Dose (DDD), or simply mg, while the indicators can be, among others, mg/Population Correction Unit (PCU), mg/kg, "Treatment frequency," or "Therapy index" (29).

Although it might seem contradictory, despite the above, Europe can arguably be seen as the leading region (33), in working toward the harmonization of methods. The significant progress and milestones achieved by the European Surveillance of Antimicrobial Consumption (ESVAC) project (such as the publication of the list of Defined Daily Dose (DDDvet)) (34) should be highlighted and recognized. Hopefully, these publications can be used as a guideline or template in other regions of the globe.

Besides the absence of consensual and harmonized units and methods, other factors have also limited the availability of AMU information:

(i)   the right incentives to motivate farmers to record on a digital format their AMU data have not yet been found, thus greatly limiting the amount and quality of data that can be accrued from these primary stakeholders;
(ii) at the moment, much of the attention is given to identify those producers that use more antibiotics (35), which might trigger fear for potential penalties and represent another obstacle to have AMU data;
(iii) despite the plethora of available technology, there is still no appropriate technology that allows for the recording of AMU data in an easy and fast way.

WHICH SOLUTIONS COULD THEREFORE BE IMPLEMENTED TO IMPROVE THE CURRENTLY NON-SATISFACTORY REALITY?

Solutions designed to collect producer AMU information (such as online platforms, apps, etc.) need to be user-friendly and tailored to the different circumstances (species, countries, languages). Additionally, it is important to include a wide range of different professionals [from IT requirement engineers to social scientists (36, 37)] right from the start to ensure that the final product meets its purpose, and has the appropriate medical and pharmaceutical framework behind it. An example of a solution could be a mobile app, that would translate verbal data from producers regarding a specific antibiotic treatment performed, into digital data on AMU. This solution would have also to accommodate the specific use of in-feed antibiotics (38–40), namely species, age group and number of animals fed.

The development of these tools needs to be implemented together with capacity building through educational programs and tailor-made training for the producers themselves to overcome any potential initial resistance or concerns they may have regarding the adoption of newtechnology.

A critical starting point should not be underestimated: if the drugs available on farm can only be purchased after an electronic veterinary prescription, this will already provide data about the "initial pool" of the drugs/antibiotics present/available at a farm (41). The next step should be the collection and recording of the information about the actual use, for example: species, age group and number of animals fed, when considering, for example, in-feed antibiotic use.

Having these (mandatory) electronic veterinary prescriptions has several prerequisites: the producer and the veterinarian must first establish a solid and trustful professional relationship, ultimately translated into an actual written contract (vs. an emergencies-based veterinary assistance). As part of this contract, veterinarians should be requested to provide (economic) feedback on the collected data, with the goal of maximizing the economic return of the farm – this will represent a major incentive for farmers to contribute to the AMU electronic data collection, giving them also an important sense of actual ownership and access of the data.

Awareness campaigns will also be another part of the solution. These campaigns should highlight the connection between AMU data and human health, by expounding the concept that providing animal AMU data not only has a direct effect and impact on animal health, but also has spillover effects on human (16) and environmental health (13). Financing such campaigns can be challenging. But AMR is a societal problem (42), for which I argue, public-private funding partnerhips should be developed out of the best interest of both parts; if it is true that the use of antibiotics/antimicrobials is mostly done in the private sector (particulary on animals) the development of resistance in humans, from animal origin, eventually leads to very significant economic expenses by the different public health authorities (43). And in reality, transmission of pathogens carrying AMR determinants can also happen in the human–animal direction (44, 45). The work by Höjgård et al. (46) suggests a societal net benefit, in the specific case of the prevention of the introduction of Livestock-associated Methicillin-resistant *Staphylococcus aureus* (LA-MRSA) into Sweden and subsequent prevention of human infections (46).

Regardless of the solutions (to increase digital AMU data availability) proposed, the likelihood of their successful uptake will certainly be increased if a bottom-up approach is adopted, whereby the livestock producers' opinions are heard and taken into consideration. Listening to all of them is obviously unrealistic, but umbrella organizations can aggregate their views and express them accordingly.

I here argue that some of the solutions that can contribute to merging the existing gap, between what would be expected, and what is the reality, when it comes to the availability of AMU digital data include:

i.   further developments of the harmonization strategy that ESVAC is pursuing;
ii.   having veterinary electronic prescriptions of the drugs available on a farm;
iii. requiring the existence of a consultancy contract between farmers and their veterinarians, as well as between feed manufacturers and veterinarians;
iv.   creating the (financial) incentives that can enhance farmers' motivations to keep digital data on their AMU;
v.   awareness campaigns highlighting the relation between AMR in humans and animals and the consequent usefulness of AMU data;
vi.   the development of user-friendly technological options.

Data are increasingly seen as the 21st century gold and, if collected and analyzed in the proper way, they can indeed contribute to our understanding and control of a societal problem such as AMR.

AUTHOR CONTRIBUTIONS

Jorge Pinto Ferreira is a Doctor of Veterinary Medicine with five years of clinical experience (food animals); a Masters in Food Safety; a PhD (as Fulbright scholar) in Public Health with a graduate certificate in Public Policy (NCSU & Duke); and a recent Diplomate of the European College of Veterinary Public Health. Jorge currently works as aconsultant at SAFOSO AG, where he has been dedicating most of his professional career to AMR. He attended the AHEAD 2017 workshop, where he presented some of the capacity building work that SAFOSO did/is doing in countries like Vietnam and Ukraine. In this perspective paper, he presents his own perspective about the different aspects related with Antimicrobial Usage (AMU), particularly the reasons behind the availability (or lack of it) of harmonized electronic digital data, and some potential solutions to overcome this.

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Authorization and Toxicity of Veterinary Drugs and Plant Protection Products: Residues of the Active Ingredients in Food and Feed and Toxicity Problems Related to Adjuvants

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Chemical substances applied in animal husbandry or veterinary medicine and in crop protection represent substantial environmental loads, and their residues occur in food and feed products. Product approval is governed differently in these two sectors in the European Union (EU), and the occurrence of veterinary drug (VD) and pesticide residues indicated by contamination notification cases in the Rapid Alert System for Food and Feed of the EU also show characteristic differences. While the initial high numbers of VD residues reported in 2002 were successfully suppressed to less than 100 cases annually by 2006 and on, the number of notification cases for pesticide residues showed a gradual increase from a low (approximately 50 cases annually) initial level until 2005 to more than 250 cases annually after 2009, with a halt occurring only in 2016. Main notifiers of VD residues include Germany, Belgium, the UK, and Italy (63, 59, 42, and 31 notifications announced, respectively), and main consigning countries of non-compliances are Vietnam, India, China, and Brazil (88, 50, 34, and 23 notifications, respectively). Thus, countries of South and Southeast Asia are considered a vulnerable point with regard to VD residues entering the EU market. Unintended side effects of VDs and plant protection products may be caused not only by the active ingredients but also by various additives in these preparations. Adjuvants (e.g., surfactants) and other co-formulants used in therapeutic agents and feed additives, as well as in pesticide formulations have long been considered as inactive ingredients in the aspects of the required main biological effect of the pharmaceutical or pesticide, and in turn, legal regulations of the approval and marketing of these additives specified significantly less stringent risk assessment requirements, than those specified for the active ingredients. However, numerous studies have shown additive, synergistic, or antagonistic side effects between the active ingredients and their additives in formulated products; moreover, toxicity has been evidenced for various additives. Therefore, toxicological evaluation of surfactants and other additives is essential for proper environmental risk assessment of formulations used in agriculture including animal husbandry and plant protection.

Keywords: veterinary drugs, pesticides, active ingredients, additives, adjuvants, surfactants, ecotoxicity

INTRODUCTION

Large quantities of various chemical compounds and their formulations are used in several fields of agriculture, such as veterinary medicine, animal husbandry, animal nutrition, and chemical plant protection, and these substances may have adverse effects on the environment. Food/feed and environmental safety of these formulated products are governed by several approaches.

Active ingredients of both veterinary drugs (VDs) and plant protection products (PPPs), i.e., pesticides are strictly regulated in the European Union (EU) regarding both their approved use and allowed level of occurrence in animal products. As for approval for use, the active ingredients are registered at EU level, while authorization of the products is carried out at EU or at Member State (MS) level. Such a dual registration protocol has certain, clear benefits, e.g., the formulated products are approved according to regional needs (ecological considerations—biogeographical regions) and also results in disadvantages (e.g., regulatory rigidity as given problems with the formulated products may not be addressed at EU level, but have to be dealt with by each MS). As for post-market monitoring, maximum residue limits (MRLs) for the active ingredients and their metabolites are defined by law in both sectors (VDs and PPPs) and are subject to official monitoring by the competent authorities, facilitated by the Rapid Alert System for Food and Feed (RASFF) of the EU.

The applied formulations may contain various additives (e.g., surfactants), besides the active ingredients, and these additives have long been classified as inert or inactive components in the aspect of the main biological effects of the formulation. Despite their name, however, inert ingredients may be biologically or chemically active in their side effect profile and are labeled as inert only because of their function in the formulated product.

LEGAL REGULATIONS FOR THE REGISTRATION OF VDs AND PESTICIDES

Authorization and distribution of agrochemicals are strictly regulated worldwide. Although these regulatory frameworks for VDs and PPPs have different historic origins, the former having roots in the legal regulations of human pharmaceuticals,

similarities, and characteristic differences exist between these two sectors. Important similarity aspects include the legal approval systems being focused on scientific evidence-based risk assessment (RA) and putting a strong emphasis on safety, primarily toward improving human health (1). Possible direct or indirect environmental risks have received increasing attention lately in both groups, yet regulatory pharmacology and toxicology of VDs are more pronouncedly oriented by a comparative medicine aspect, then the assessment of PPPs.

Veterinary Drugs

Extensive control of VDs is required in the EU, and thus, the requirements are very strict not only for quality and efficacy but also for safety, including animal and human health and environmental risk assessment (ERA), similarly to the assessment and regulation of human medicines. Upon revision, veterinary legislation Directives 81/851/EEC and 81/852/EEC (2, 3) were amended by Directives (EEC) 2004/28 and 2009/9 (4, 5). Specific directives and legal specifications regulate the distribution and required quality of veterinary substances, including veterinary medical products, ready-made veterinary products, blood products, and homeopathic preparations (2, 6, 7), while immunological veterinary medical products, medicated feeding stuffs and premixes, and biocidal products used for veterinary hygiene are regulated elsewhere. In the EU, two main processes are available for authorizing veterinary medicines: a centralized EU procedure and national protocols. In the centralized procedure, medicinal products are authorized at EU level by the European Medicines Agency (EMA), established in 2004 (6). At national levels, medicines are authorized by MSs in their own territory on the basis of either their own RA or RA carried out in another MS if accepted on the basis of mutual recognition or the decentralized procedure (4, 7). The conditions of marketing authorizations for medicinal products for human and veterinary use are set by Regulation (EC) 712/2012 amending Regulation (EC) 1234/2008 (8, 9). The health RA and ERA requirements of veterinary pharmaceuticals include and ensure the safety of the patient, the user, the products used for food producing animals, the consumers, and the environment, as well. The major aspects of health RA and ERA are quality (e.g., composition, stability, and shelf-life), safety [e.g., consumer safety and residues (only for food producing animals), user, patient, and environmental safety], and efficacy (e.g., pharmacodynamics, pharmacokinetics, laboratory studies, and clinical trials). RA of VDs is carried out on a continuous basis also upon the approved commercial distribution of the preparations, and product quality, efficacy, and safety are routinely monitored by the regulatory and monitoring authorities (1). Pharmaceuticals used in VDs are tested on target species at the therapeutic dose and at its multiples. MRLs for VDs are set by Regulation (EC) 470/2009 (10) that replaced and repealed Regulation (EEC) 2377/90, introducing number of modifications and improvements (11). The regulation of MRLs for VDs includes any ingredients used in veterinary pharmaceuticals and vaccines with pharmacological or pharmacodynamic activity; therefore, evaluation of stabilizers, antioxidants, solvents, and coloring agents is also required. The overall purpose is to ensure the protection of consumers from potentially harmful drug residues in food of animal origin. Pharmacovigilance is an integral part of

the regulation for both veterinary and human medicines in the EU, used to describe the collection of information on the adverse effects of pharmaceutical agents (12).

Plant Protection Products

Plant protection products are governed in the EU by Regulation 1107/2009 (EC), the "Pesticide Act" (13). A rather important feature of the pesticide registration policy is that pesticide active ingredients are authorized at the EU level, while formulated PPPs and their uses on given crop commodities are registered at MS level. The active ingredients must be approved for use by the European Commission (EC) to be considered for being marketed in any form of pesticide formulations. In the process of authorization, these substances are evaluated in scientific evidence-based RA by the European Food Safety Authority (EFSA), established in 2002 (14). RA statements issued by EFSA, debated, and commented by the MSs are the basis of the subsequent EC decisions regarding authorization. Active ingredients classified as carcinogenic, mutagenic, teratogenic, endocrine disruptor, persistent, and bioaccumulative substances cannot be approved (15). Pesticide active ingredients regularly undergo detailed reassessment, and during the last major re-registration process, completed in 2010, the number of the registered active ingredients has substantially been reduced from 959 to approximately 480 compounds authorized now as pesticide active ingredients in PPPs (16).

In contrast to pesticide active substances, formulated PPPs are authorized by the MSs on their territory, in accordance with the corresponding EU rules and regulations. Moreover, the enabled use of the pesticide formulations in various crop cultures is determined at MS level, as well.

To avoid over-excessive human exposure to pesticide residues through foodstuff and the drinking water, MRLs have been established for these compounds in different commodities throughout the world, including the EU, and the levels of pesticide residues are required to be regularly monitored. MRL values are set by the EC for all food and animal feed categories on the basis of a complete RA by EFSA (17). If the levels of residues in case of approved pesticides exceed the determined MRLs in the food and animal feed products, measures have to be taken to prevent the use of the contaminated products/crops. In contrast, previously permitted, but later withdrawn or banned active ingredients of pesticides or their metabolites cannot be present in the food or animal feed at any concentration. These contaminants are usually originated from inappropriate technology or earlier environmental contamination. The official MRLs of pesticide residues are specified in *Codex Alimentarius* (18) and other declarations (17, 19) for various commodities.

As mentioned earlier, PPPs as pesticide formulations are subject to dual approval: registration of their active ingredients at EU level and authorization of the formulated product at MS level. Both levels rely on the determination of physico-chemical, toxicological, and ecotoxicological properties of the substances (the active ingredient or its mixture with its adjuvants), and data determined are used in scientific evidence-based ERA on the basis of both the Pesticide Act and Regulation 1907/2006 (EC), the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) Act, supervised by the European Chemicals

Agency (ECHA), established in 2006 (20). The legal framework for the authorization of feed additives and biocides (falling outside the main scope of this paper) substantially differs from the legal regulation of PPPs. Regulation (EC) No 1831/2003 on additives for use in animal nutrition (21) regulates the placing on the market and use of feed additives and premixtures, including their supervision and labeling. The EU Register of Feed Additives (22) compiled on the basis of this regulation lists numerous types of additives, including emulsifying and stabilizing agents, binding, anti-caking agents and coagulants, preservatives, antioxidants, acidity regulators, enzymes, digestibility enhancers, gut flora stabilizers, coccidostats and histomonostats, microorganisms, silage additives, mycotoxin binders, colorant and flavoring compounds, carotenoids and xanthophyllsm, (pro)vitamins, amino acids, and trace elements. Regulation (EU) 528/2012 the Biocidal Product Regulation (23) concerns the placing on the market and use of biocidal products used to protect humans, animals, materials, or articles against harmful organisms, e.g., pests or bacteria, by the action of the active substances contained in the biocidal product. Although the current paper focuses on VDs and PPPs and does not intend to discuss these two additional groups of products (feed additives and biocides), it has to be noted that given active ingredients may be subject to different legal requirements, when used as VDs (assessed by EMA), "hygienic substances" (biocides) (assessed by EMA or ECHA), or PPPs (assessed by EFSA), which remains a residue contradiction of the current legal setup in the EU (24). In addition, certain toxicity tests required to register PPPs are often performed with the active ingredient alone, not with the pesticide formulation itself. Moreover, ingredients inert in the main effect of the preparation are generally not even indicated on product labels and are often claimed to be confidential business information. This is an improper practice, as "inert" ingredients can significantly affect toxicity endpoints, including developmental neurotoxicity, genotoxicity and disruption of neuroendocrine functions. This phenomenon remains to be another major contradiction in the scope of the legal regulations of pesticides and other biologically active substances (biocides).

Registration Requirements for Formulation Additives

On the basis of the current legislation, substantially simpler ERA is sufficient for these substances compared to the active ingredients. For example, specific product characteristics (SPC) have to be specified for all components, but the exact percentage quantity of the formulation additive is not required to be specified as public information. SPC has to be quantitatively stated for active ingredients, but the exact content of formulation additives can be specified as proprietary information released only to the registration authorities as classified information in the products documentation. Nonetheless the ERA is specified for formulation additives, as well. The main steps of ERA, similar to the assessment of active ingredients, are hazard identification (e.g., chemical structure and physico-chemical properties), assessment of the exposure [determination of the predicted environmental concentration (PEC), biodegradability assessment] and the effects [acute and chronic toxicity, sub-lethal effects, determination

of the predicted no-effect concentration (PNEC)], as well as characterization of the risk on the basis of the ratio of PEC and PNEC (25, 26). The conditions of the ERA are determined by Regulation (EEC) 793/93, Directive (EEC) 93/67, and Regulation (EC) 1488/94 (27–29). The conditions of the authorization and commercial distribution of surfactants (e.g., detergents) in the EU are set by Regulation 648/2004 (EC), adopted on March 31, 2004, and came into force on October 8, 2005 (30), but it focuses primarily on general-purpose surfactants used in laundry detergents and cleaning supplies. As for surfactants in laundry detergents and cleaning supplies, requisites for anionic and non-ionic surfactants regarding primary biodegradability are set in the regulation. Moreover, on the basis of the safeguard clause, if a given surfactant (e.g., detergent) is considered as a risk to human or animal health safety or to the environment by one of the MSs, temporarily special conditions or the proscription of the commercial distribution of the products containing the adverse component can be applied on the area of the given MS. However, RA applies only for surfactants used in laundry detergents and cleaning supplies, and requirements are not as strict as those for biologically active ingredients.

With the introduction of the legal framework of the REACH Act, the EU regulatory system became stricter, and scientific evidence-based RA has been set as a legal requirement to commercialized chemicals (4, 20). Moreover, due to the recognized potential increased toxicity of chemical mixtures, compared to their individual components, the classification, labeling, and packaging of chemical mixtures (e.g., detergents) are specifically regulated by law in the EU (15); and health RA and ERA of additives (e.g., detergents) became substantially more compliant with the RA of the active ingredients.

Currently, the exact chemical name and quantity is legally required to be indicated on the labels of pesticide formulations in the EU only for the active ingredient(s), synergists, and antidotes; therefore, the exact composition and information about adjuvants is not public.

SAFETY ASSESSMENT OF THE ACTIVE INGREDIENTS

Safety assessment of agrochemicals is an issue of emphasized importance worldwide. The establishment of the food and feed control system at EU level started in 2002 with Regulation (EC) 178/2002 laying down the general principles and requirements of food law, establishing EFSA and laying down procedures in matters of food safety (14). This was followed by a set of regulations on hygiene (31–33), and then Regulation (EC) 882/2004 on official controls performed to ensure the verification of compliance with feed and food law, animal health and animal welfare rules (34). The former separated units, independent authorities, and institutes adopted the food production, trade, and consumption chain approach covering the entire food chain from the farm to the table and enhancing follow-up and prevention. These regulations—to assure high level health and consumer protection—established a new, prevention approach in the food/feed policy. The aim of both the legislative and the advisory systems was utilization of

an integrated, "from farm to fork" approach, covering the overall food chain including feed production, primary food production, processing, storage, transport, and trade.

The EU RASFF

National food safety authorities of the MSs of the EU officially monitor agricultural produce, as well as food and feed commodities for compliance with the current official MRLs of residues of agrochemicals, including VDs and PPPs. To facilitate information exchange among MSs and to the public, RASFF was established in the EU in 1979 (35, 36). RASFF operates in all EU MSs through their national food safety authorities. The system operates on the basis of authority statements on execution measures of the alert system for food and feed safety. Within the system, MSs report to the EC, without delay, any hazards affecting animal and human health directly or indirectly originated from food and feed products or commodities that have been identified through RASFF. The system, operated by the EC, establishes a direct contact among the EC, EFSA, and relevant authorities of the MSs. Any identified hazard related to food and feed and reported to the EC is promptly transferred to all RASFF members. To date, RASFF has been proven to be an effective instrument to exchange information in real time within EU MSs. RASFF is a prominent device to report non-compliances in agricultural commodities and food products with food/feed safety regulations to ensure a direct and real-time exchange of information among countries in the EU and to assist sustenance of an outstanding food/feed safety status.

Data are submitted to the RASFF by National Reference Laboratories (NRLs) in each EU MS and contributing countries. NRLs for the detection of residues are listed in Commission Decision 98/536/EC (37) and Implementing Decisions that followed it, including the latest Regulation 2017/625 (EU), which is the new legal framework for control in food, feed, animal, and plant health (38). High-quality and uniform testing operation of the NRLs is ensured by EU Reference Laboratories (EURLs) governed by Regulation (EC) No 882/2004 on official controls regarding tasks, duties and requirements (34). The EURLs provide NRLs with analytical methods and diagnostic techniques, coordinate their application, train NRL staff, provide the EC with scientific and technical expertise in relation to laboratory analysis, and collaborate with the competent laboratories in non-EU countries. This concerted action of the reference laboratories at EU and national levels assures continuous improvements in the detection capabilities and accuracy within RASFF. Additional sources of improvements in the analytical performance include the introduction of new detection techniques within the range of tools used by NRLs, on one hand, and the expansion of the EU MSs, on the other hand. Advances achieved in method development in food analysis are implemented among the qualitative and quantitative screening and confirmatory tests used at NRLs, and in addition to spectroscopic and chromatographic instrumental methods, functional and biochemical assays, immunoanalytical techniques (immunoassays, immunosensors) and nanoparticle analysis (39) are assessed to expand the range of available methods in food analysis for competent authorities. Moreover, "foodomics" (40), high-throughput analysis (41), and "big data" analysis (42) are also implemented to facilitate food safety. Such

analytical progress results in not only the expansion of analysis capacities but also increasing analytical sensitivities and lower limits of detection. Similarly, the enlargement of the EU through the accession of new MSs broadens the residue analysis laboratory network under the Directives 96/23/EC (43) and 98/536/EC (37) reporting to RASFF, improving both its analysis capacity and overall accuracy.

The evolving organization of laboratories involved in the activities of RASFF explains the evolution of the number of contamination cases reported in RASFF. The EC established RASFF with the aim to identify and publicize products on the food market and their producers, distributors violating food/feed safety requirements (44). The database containing analytical results was officially established in 2002 (14), but preliminary data are reported since 1998. Analytical instrumentation of sufficient limits of detection and sample capacity has become available since 2003, since when annual fluctuations are trustworthy. Moreover, analytical determinations have been accompanied by RA since 2011 (36), the decisional system of which is becoming stabilized only gradually, generally becoming stricter.

Searchable databases, summarizing nearly 47 thousand notifications reported until now, 34% of which corresponding to the period of 2012–2016, available at the official Internet portal of RASFF, reflect the current state of imported food/feed commodities in the EU (45), although the overall number of samples analyzed annually, which could provide a view on the real significance of a given problem, is not specified. It is apparent from the Annual Reports of RASFF, e.g., the Preliminary Annual Report 2016 (46) that the number of notifications continues to increase in all notification categories, including alerts, border rejections, information for attention, and information for follow-up. Notifications expanded by 52% between 2006 and 2016, with substantial (17%) increase in border rejections, possibly due to Regulation (EC) No 669/2009 (47) imposing stronger border controls on food of non-animal origin, with systematic checks on documents accompanying all (100%) consignments, and routine physical checks, including laboratory analysis, at a frequency related to the risk identified. Certain notifications may correspond to the same sample, if multiple contaminants were above the official threshold of notification or intervention.

Rate of Occurrence of VDs and PPPs as Contaminants in Europe

The four most prevailing causes of notifications in RASFF, representing over half of all notifications are mycotoxins, pathogenic microorganisms, pesticide residues, and heavy metals. Other causes are related to processing or treatment (e.g., foreign materials, non-pathogenic microorganisms, improper storage conditions, deviations in flavor and odor, and poor packaging) or deviations from legal requirements (e.g., improper composition, lacking documentation, non-declared allergen content, and erroneous labeling).

A comparative analysis of violations found in RASFF for VDs and PPPs is rather informative. The overall numbers of RASFF notifications regarding VD and PPP residues between 2002 and 2016 were 2,036 and 3,527, respectively, indicating not only a 72%

higher occurrence rate for pesticide residues but also different temporal trends. VD residues are a group of contaminants of lesser importance than the four groups mentioned earlier, as residues of pharmaceuticals (human and veterinary combined) represent only 4% of all notifications and are ranked 7th among the causes of notifications. This relative ranking remained unchanged in the period of 2012–2016 (behind pathogenic microorganisms, mycotoxins, pesticide residues, heavy metals, additives, and contaminant migration), 46, 19, and 35% of which were severe, undecided, and non-severe cases, respectively. While the initial high number of reported cases in 2002 for residues of VDs has successfully been pushed to a level below 100 cases annually (**Figure 1A**), the number of reported violation cases for pesticide residues occurred to display a gradual increase from a low (approximately 50 cases annually) initial level after 2007–2010, and this tendency has come to a visible halt only by 2016 (**Figure 1B**). The opposing tendencies between the two sectors may be explained by their differing toxicology background: the toxicological requirements that apply for residues of human pharmaceuticals often provide substantial basis also for the assessment of VD residues, while such considerations are less expressed for pesticide residues. Toxicological rigor could effectively limit improper practices through firmness and proportionality of the measures taken in the regulation of veterinary medicine, unlike in the sector of pesticide residues. The difference became even more visible after 2012, when monitored data became subject to additional
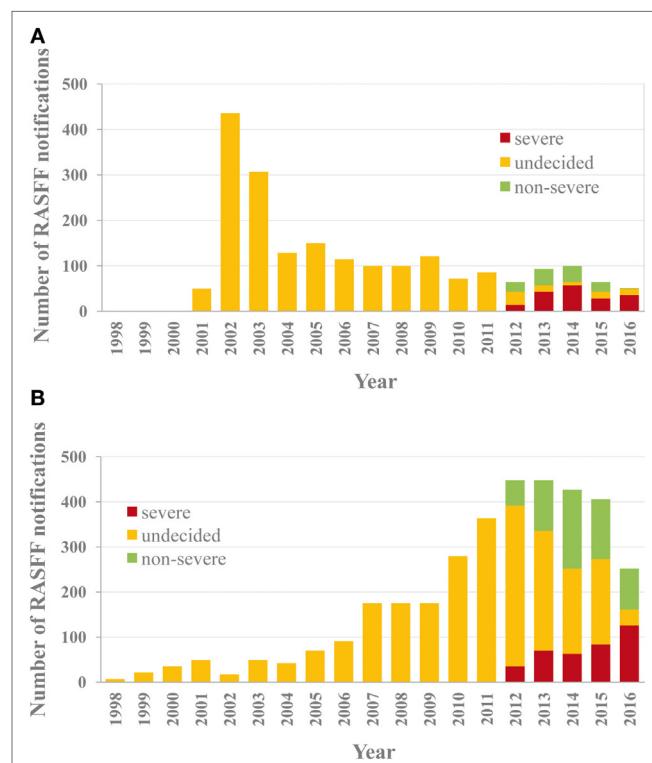

FIGURE 1 | Notifications regarding residues of veterinary drugs **(A)** and pesticide residues **(B)** in agricultural products between 1998 and 2016 in the Rapid Alert System for Food and Feed (RASFF) database. The proportion of assessment-based risk severity decision categories is indicated after 2012.

RA in RASFF. While the proportion of the category of "uncertain severity" decreased below 20% shortly after the introduction of the additional RA in RASFF (**Figure 1A**), it lengthily remained at 50% for pesticide residues, and this persisting tendency could be reversed only by 2016 (**Figure 1B**), also seen in the number of the documented cases. Uncertainty in decision-making can obviously not suppress improper practices effectively, as it cannot give ground to proportional measures taken.

The residues of the persistent active ingredients used in veterinary medicine repeatedly reach susceptible environments and habitats. It is quite common that pharmaceuticals already considered improper for humans still remain in use for a while as VDs and, in turn, still can reach the human body via food products of animal origin. Such cases were seen in the eighties for chlorinated hydrocarbons (not indicated by RASFF) and also lately for antimicrobials, the latter having been of growing concern regarding antimicrobial resistance appearing as a response to increasing chemical pressure on the environment due to antimicrobial VD residues (48, 49), particularly as antimicrobial resistance is known to emerge due to various environmental drivers (50) that should be a key policy aspect for environmental regulators. Numerous violation cases were recorded in RASFF in 2002–2003, when extensive monitoring was launched, and these cases were mainly related to crustaceans and other marine animals from aquacultures of Southern and Southeast Asia, and the safety status of the derived food products could be normalized only by 2010. The same can be said about apiculture products: the ban of honey import from China to the European market in 2009 resulted in a significant improvement in food safety. Similar spectacular advancements took place among poultry and fish products in 2004 and 2008, respectively. A different trend occurs, however, for mammalian farm animals, where numerous problems remain to occur in food production (e.g., pig, beef, and horse meat).

A detailed analysis of VD residues is most expedient to be carried out for the 2002–2005 period (**Figure 2**), when the largest number of notifications was issued. The corresponding period for pesticide residues is 2011–2015. Major countries of origin that have been identified as leading sources of notifications during the entire period of RASFF are Vietnam, India, and China, followed by Brazil, Thailand, and Bangladesh. As seen, countries of Southern and Southeast Asia are most frequently associated with questionable safety of food products of animal origin. Leading EU MSs as sources identified for VD residues in food products are Belgium, Poland, and Lithuania. It has to be mentioned, however, that these countries may be identified as contamination sources as importers.

Analysis of the 2002–2005 and 2012–2015 periods allow different conclusions regarding VDs. More than a decade ago, the overall incidence of nitrofuran type antibiotics was the highest in food products of animal origin, but individual occurrence of the dichloroacetic acid derivative chloramphenicol was the highest, and aminoglycoside streptomycin also occurred, although with substantially lower incidence, among notifications, moreover, several sulfonamides were detected. The most common within this last chemical type has been sulfathiazole, commonly used, in spite of its ban, in apiculture in China. Finally, malachite green

(along with its metabolite in animals, leucomalachite green) and crystal violet (also known as gentian violet, previously used in aquaculture) can also be mentioned as contaminants detected.

Nitrofuran antibiotics are of outstanding significance among VD residues. Furaltadone [and its metabolite, 3-amino-5-morpholinomethyl-2-oxazolidone (AMOZ)] frequently occurred in poultry meat (e.g., chicken and sometimes turkey) from Brazil and occasionally from Thailand. The occurrence of furazolidone [and its metabolite, 3-amino-2-oxazolidinone (AOZ)] has been high in crustacean and fish shipments from South Asia, in egg products from India, pig and rabbit products from China, chicken from Thailand, and honey from Argentina. Residues of nitrofurazone [and its metabolite semicarbazide (SEM)] were common in freshwater shrimp from South Asia, lyophilized egg powder from Brazil, India, and France, chicken from Brazil and Thailand, and pig and rabbit from China.

Among antibiotics, chloramphenicol is known to widely occur in apiculture products. In addition, it has been detected in dairy products and commonly occurred in crustaceans and fish. Moreover, it has been detected in rabbit and duck meat and pork from China and duck meat from Thailand, as well as in duck and goose feed in Germany, which may explain the current situation.

Several changes have taken place by 2012–2015. The detection rate of AMOZ has decreased to a minimal level, and the statistics of AOZ occurrence has also improved, although the latter compound remains to occur in shrimp from Asia (India, China, and Malaysia) and rabbit from China. As a new emergence, it occurred in calf meat and also in animal feed above MRL in the Netherlands. The occurrence of SEM also shows a more favorable pattern by now, but as a new feature, it appeared in beef from Brazil and is a common contaminant of pangasius fish from Vietnam. As a result, the reputation of this fish, very well tolerating dense rearing conditions and only slightly sensitive to water contaminants, is rather unfavorable. The improvements are significant for the residues of chloramphenicol as well. Its incidence in apiculture products has dropped to casual occurrence after honey from China has been forced out from the EU market. The same applies to other antibiotics as well, indicating that one of the greatest successes in European food safety has been the regulation of apiculture products. Nonetheless, occurrence of chloramphenicol remains detectable in shrimp from China and Vietnam, as well as pork from China. Moreover, as it is still found in feed components from Belgium, France, and India, its casual occurrence has been indicated in various meat samples.

It has to be noted that in spite of the severe restrictions in the use of antimicrobials, the annual sales (and in turn, the anticipated usage) of these drugs remain high in Europe, particularly in Spain, Cyprus, and Italy, as reported by EMA in 2014 (51), and differences among countries in the use of antibiotics can be explained by different national regulations, prices, climate conditions, and animal demographics, as well as dosage regimes and the veterinarians' prescribing habits. Among non-steroid anti-inflammatory drugs, residues of phenylbutazone in horse meat used for the treatment of the common degenerative disorder, chronic arthritis in horses, emerged as a new problem. The use of phenylbutazone has been substantially limited in the United Kingdom (UK), and it is currently registered for the treatment
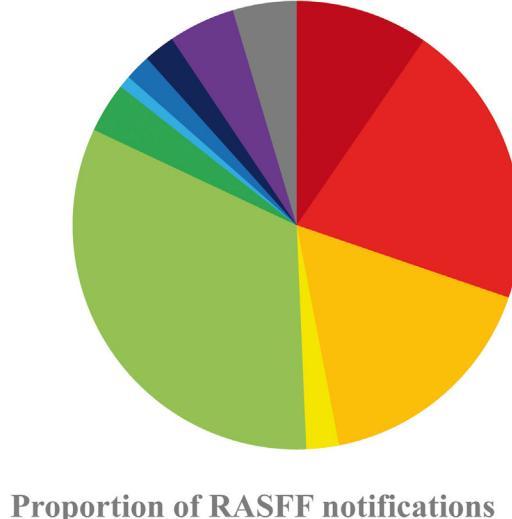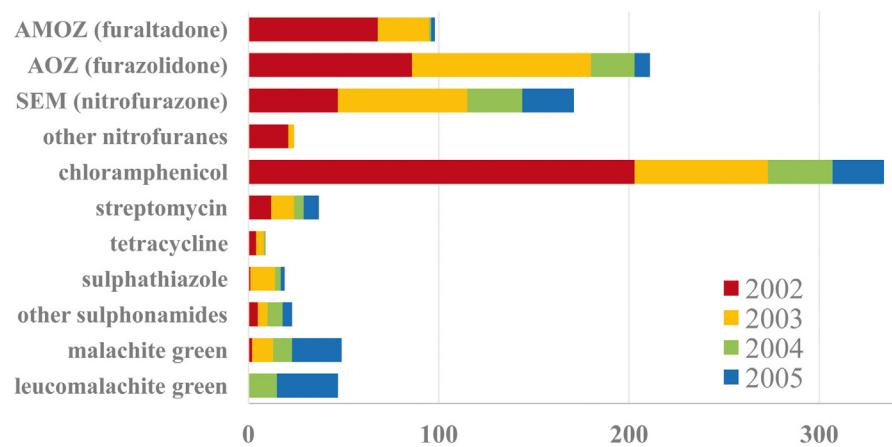
FIGURE 2 | Frequently reported active ingredients of veterinary drug (VD) residues in the Rapid Alert System for Food and Feed (RASFF) database in the corresponding critical period, 2002–2005 (above). Proportions of the VDs reported during the 4-year period (below).

of race horses only. However, it can strongly be anticipated that this food safety problem, used to remain hidden due to the lack of control, existed before as well.

Feed additives are listed in a separate database within RASFF. The few cases detected (55 cases between 2012 and 2016) were limited to the poultry industry and mostly to residues of clopidol (48 of the 55 cases) used against coccidiosis and no longer permitted in the EU. No growth promoters are listed among the contamination cases found, which hints to the possibility that specific monitoring of these substances may not be sufficiently effective. It is well known that weight gain in cattle is promoted in the USA by the use of beta-blockers (e.g., ractopamine) that being one of the neuralgic points of the currently on-going Trans-Atlantic Trade and Investment Partnership negotiations. The use of the two best-known non-hormonal veterinary growth promoter

preparations ZILMAX (zilpaterol—Merck & Co.) and OPTAFLEXX (ractopamine—Eli Lilly Co.) is not approved for animal husbandry in the EU, and ractopamine has been found in a horse meat sample from Mexico, as well as in beef liver from Canada according the RASFF database. Zilpaterol has been detected in horse meat from Mexico and surprisingly in poultry from Poland. In turn, wide scale monitoring of animal feed appears to be a problem that needs to be solved, as it would serve as an excellent prevention measure of contaminant dispersion.

The most complex issue in the RASFF database from the aspect of analytical determination and assessment is unquestionably represented by pesticide residues. Initial findings indicated severe warning signs as early as in 2002, immediately after the launch of the operation of RASFF, yet pesticide residue levels remained to display a trend of continuous increase until recently. This segment

with over 75 severe cases as an average annually on the basis of the last five years (2012–2016) is likely to be considerably underestimated among food safety hazards. The majority of the findings have been related to pesticide active ingredients not enrolled on the EU positive list of registered compounds. Related PPPs, however, may be legally used in exporting non-EU countries, and therefore, their residues may be found in feeds or in foods of animal origin produced there. In such cases, shipments with any detectable amounts of the given residue are rejected, even if the level remains below the earlier MRL. The other large proportion among RASFF findings correspond to the occurrence of residues of pesticide active ingredients registered in the EU, above the corresponding MRLs. Approximately two-thirds of pesticide residues reported by RASFF between 2012 and 2016 belonged to the first group, i.e., disapproved shipments were contaminated with residues from technologies no longer applicable within

the EU, and only one-third of the reported pesticide residues belonged to active ingredients authorized in the EU. Moreover, the proportion of RASFF notifications among the target analytes specified appears to be quite even. The most severe current cases of residues of banned pesticide active ingredients include carbendazim (fungicide), carbofuran, dichlorvos (zoocides), and ethephon (ripening accelerator), as well as still authorized active ingredients dimethoate and chlorpyrifos (zoocides) (**Figure 3**). A recent, severe, but isolated issue has been the case of insecticide fipronil found in eggs and egg products in 2017. Fipronil is used both in VDs and PPPs. Its veterinary use is against fleas, mites, and ticks mostly on dogs and cats, e.g., in formulated VD products Frontline, Fiproguard, Flevox, Petarmor, and Sergeant, but Frontline has been approved for poultry, for bird and housing treatments for external parasites as well, and possible emergence of fipronil residues in eggs is known since 2001 (52). In PPPs, it is
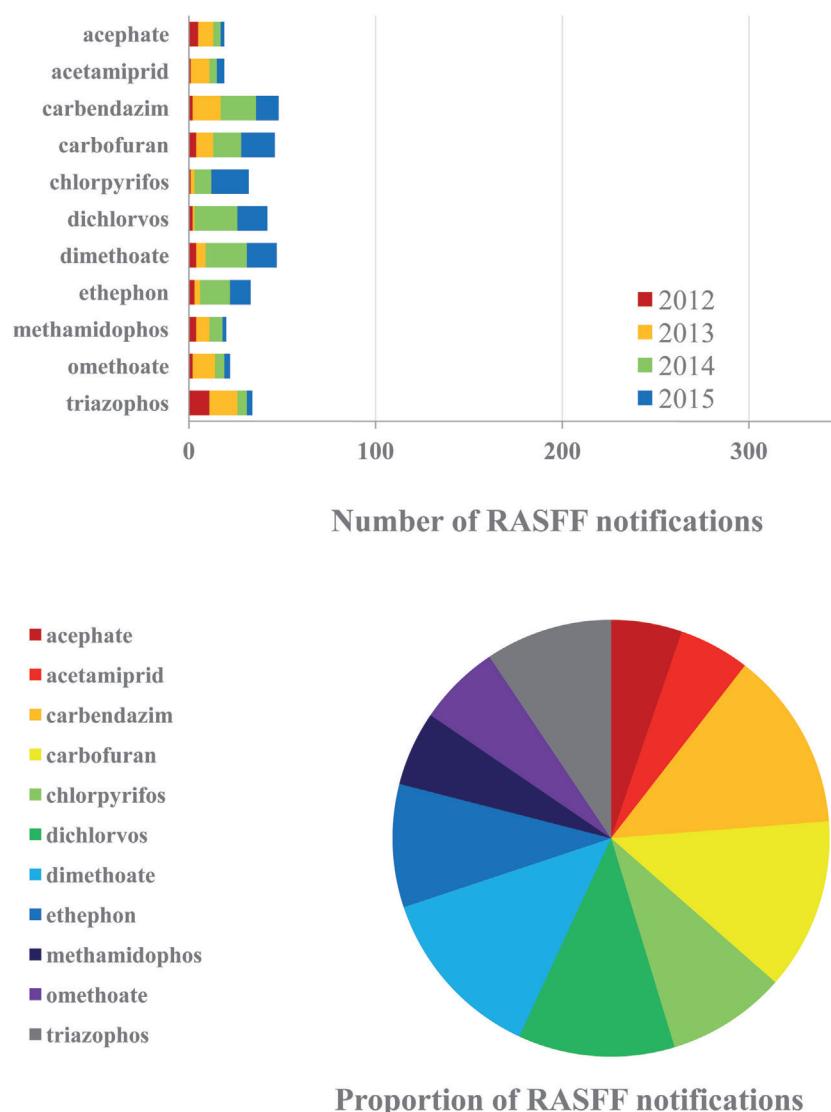
FIGURE 3 | Frequently reported active ingredients of plant protection product (PPP) residues in the Rapid Alert System for Food and Feed (RASFF) database in the corresponding critical period, 2012–2015 (above). Proportions of the PPPs reported during the 4-year period (below).
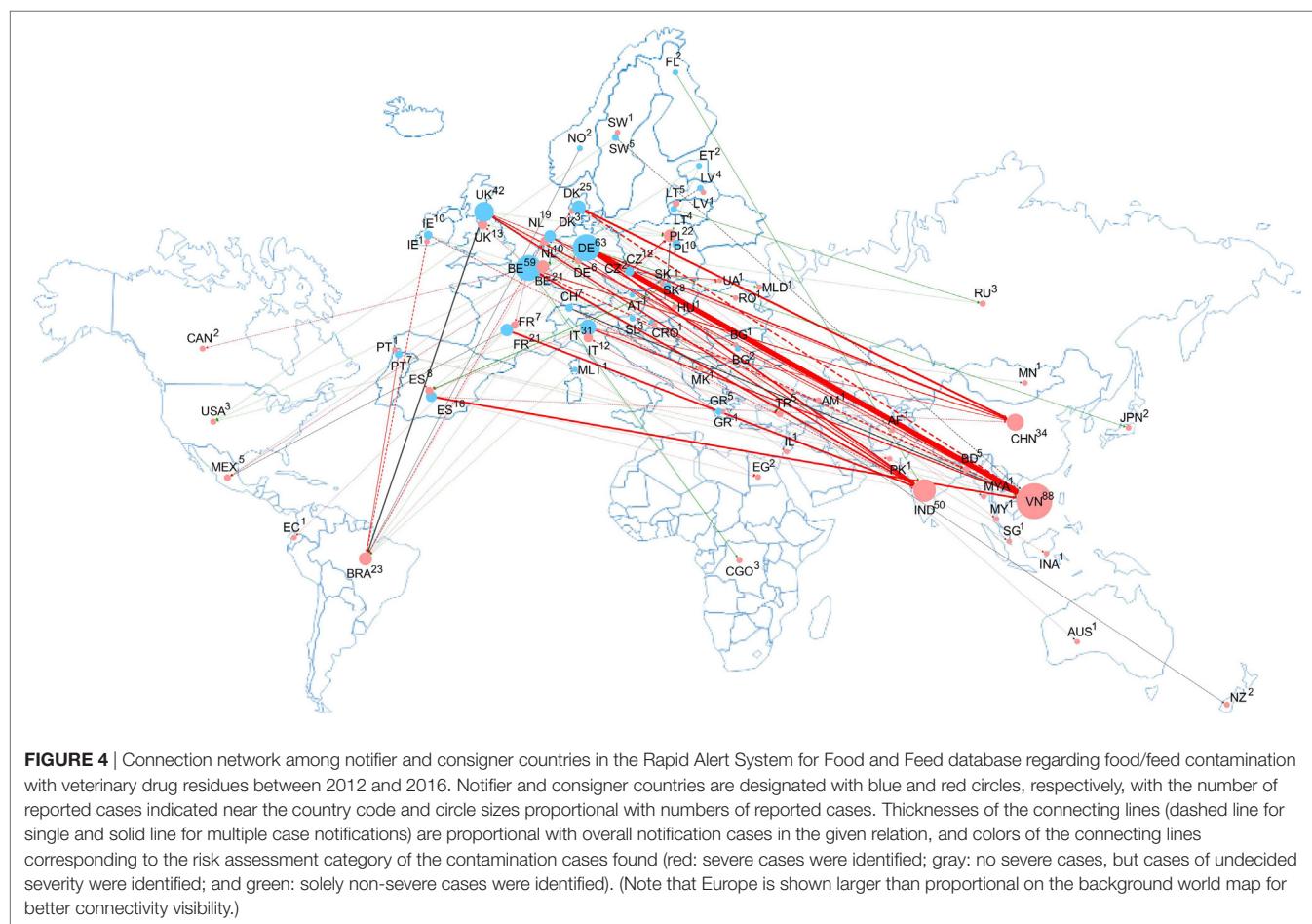
used against a wide range of insect pests. After gradual limitations of its use (e.g., strictening the use of its formulated product Regent in Hungary in 2008), fipronil was banned in the EU in 2013 from use on animals destined to enter the food chain. Over the years, residues of this insecticide have been found in commodities of plant origin (notified in most cases as border rejection), yet it was found in eggs from Belgium in 2017 at concentrations up to 1.2 mg/kg (notified as an alert of serious risk), indicating illegal use of this substance in the poultry sector and possible human health risk from contaminated eggs.

Network Analysis of the Non-Compliance Cases Reported in the EU RASFF

Mapping non-compliance cases and alerts in RASFF regarding VD residues in food and feed among EU countries and food/feed supplier countries is an informative tool in identifying the sources of non-compliances on the EU markets, if the consigner country of the notification is indeed the country of origin. It has to be noted, however, that contamination is not always detected immediately at source, and in such cases, the consigner country is an importer that further exports the commodity reported in RASFF. Claims may be (and are mostly) related to products originated from outside the EU. **Figure 4** summarizes and illustrates

RASFF notifications on VD residues in food and feed in the EU in the period when notifications are the most informative, supplemented by RA categorization (between 2012 and 2016). The network of the notification cases not only illustrate the actual relations of complaints but also provide a more accurate picture of the control system within the EU. The network map shows that most non-compliance cases were identified in relation to Vietnam and the main notifiers were Germany and Belgium.

Within the 5-year period between 2012 and 2016, there occurred 362 notifications, 67 (nearly one-fifth) of which were domestic notifications (with the notifier and consigner country being the same), indicating either domestic production or unidentified import. With this value, residues of veterinary pharmaceuticals ranked 7th (among all notifications, 168 cases, 46% of all cases were assessed as severe). Consigning countries of extensive non-compliances included Vietnam, India, China, and Brazil (88, 50, 34, and 23 notifications, respectively). Vietnam scores particularly poor in the notifications regarding VD residues, as otherwise the country is ranked at a much better, 14th position in the overall RASFF notifications from 1998 until the first quarter of 2017 (1,296 notifications). As for the other three countries, China, India, and Brazil are ranked 1st, 3rd, and 12th in the overall RASFF notifications (nearly 5,540, 2,966, and 1,618 notifications, respectively). The relative ranks of the overall

FIGURE 4 | Connection network among notifier and consigner countries in the Rapid Alert System for Food and Feed database regarding food/feed contamination with veterinary drug residues between 2012 and 2016. Notifier and consigner countries are designated with blue and red circles, respectively, with the number of reported cases indicated near the country code and circle sizes proportional with numbers of reported cases. Thicknesses of the connecting lines (dashed line for single and solid line for multiple case notifications) are proportional with overall notification cases in the given relation, and colors of the connecting lines corresponding to the risk assessment category of the contamination cases found (red: severe cases were identified; gray: no severe cases, but cases of undecided severity were identified; and green: solely non-severe cases were identified). (Note that Europe is shown larger than proportional on the background world map for better connectivity visibility.)

notifications for these four countries remained unchanged also regarding the complaints received between 2012 and 2016, and as for their RA, those assessed as corresponding to severe risk represented 30–55% for these countries. For VD residues, the overall severity rank increased from 2012 to 2014, but later displayed a favorable decreasing trend along with a parallel decrease in the number of all notifications. The network is dominated by a Germany—Vietnam axis (31 notifications, 11 of which were severe), along with strong notification connections also at other source countries mentioned above. The notifications toward Vietnam were assessed predominantly as severe by Spain, Italy, the Netherlands, and Switzerland and to a less degree by Germany, Belgium, and the UK. Predominantly severe notifications were reported toward India by Belgium, France, and the UK, with less severity from Germany. Thus, countries of South and Southeast Asia are considered a vulnerable point with regard to VD residues entering the EU market.

Although the RASFF documentation reports notifications only, and not the overall number of samples analyzed, it indicates that lead monitoring EU countries for all food and feed contaminants on the basis of their reported notifications are Italy (7,981 RASFF notifications from 1998 until the first quarter of 2017), followed by Germany, the UK, Spain, the Netherlands, France, Belgium, and Denmark (6,571, 5,130, 3,741, 3,180, 2,671, 1,782, and 1,540 notifications, respectively). These same countries were reporting the highest numbers of VD residues found between 2012 and 2016 but in a slightly different order: Germany, Belgium, the UK, Italy, Denmark, France, the Netherlands, and Spain (63, 59, 42, 31, 25, 21, 19, and 16 notifications, respectively). The numbers of notification cases in the official monitoring in each country indicate that not only the operation of the food safety sector at the European level is a determining factor, but the national food safety organizations, of which the Federal Institute of Risk Assessment (BfR) in Germany is of outstanding weight, also represent an equally important contribution. It has also to be noted the non-EU countries, particularly Norway and Switzerland, also provide data to the RASFF database.

The Range of Target Analytes in the EU RASFF

Rapid Alert System for Food and Feed monitors food/feed contaminants according to its legal mandate: its target analytes include pathogenic and non-pathogenic microorganisms, mycotoxins, PPP, and VD residues, allergens, foreign materials, industrial and biocontaminants, food and feed additives, as well as improper compositions, genetically modified components or adulteration. These contaminants, covered within the RASFF activities are regulated by legal MRLs, threshold levels or critical content for mandatory labeling. The MRLs specified, e.g., in Regulation (EC) 470/2009 (10) apply only to pharmacologically active components but not to "inert" substances. In turn, RASFF does not cover excipients, because these components are—often erroneously—considered "inert" substances. They are, indeed, inert *per definitionem* in the main effect of the formulation they are used in, but they may also exert adverse side effects. Emerging information on the hazards of risks related to formulant additives indicates that some of these

excipients should be included among target analytes in RASFF; in other words, MRLs should be defined for these substances as well. The EU-wide regulation of adjuvants and co-formulants is being planned; however, their monitoring is hindered by the facts that analytical methods for their determination are often missing, and quantitative analysis is often problematic for these complex, in given cases not fully described substances. Moreover, the effect of these excipients on the residue levels recorded for the active ingredient is hardly studied.

EXCIPIENTS, ADDITIVES, AND ADJUVANTS

Beside the active ingredients, several additives can also be found in formulated animal therapeutic agents and feed additive products, as well as in the formulated pesticide preparations. Among additives, classified into several groups by their function, adjuvants are a minor group of substances, used for the primary purpose to enhance the biological effect of the active ingredient (13, 53). Thus, adjuvants (e.g., various surfactants, solvents, dispersing agents, activators, wetting or antifoaming agents, anti-evaporants, drift retardants, softeners, safeners, stabilizers, and penetrants) directly affect the efficiency of the formulations. Further groups of additives are not used for the purpose of amending formulation efficiency but implement other purposes related to application, such as the promotion of safe use and application ensured by colorants and odorants (54). For example, the warning effect of the red dye used to be applied in carbofuran-based formulations or the unpleasant smell of odorants applied in obsoleted formulations containing paraquat or diquat used to serve the purpose of lowering the possibility of human poisoning during use and application of the formulations (55, 56). Additionally, other groups of additives consist of various trapping agents and attractants, which also do not affect directly the efficiency of the active ingredient (13, 57, 58). As seen from the above, the often seen practice of using additives and adjuvants as synonymous words is incorrect.

Surfactants

A characteristic feature in the chemical structure of different surfactants is the simultaneous presence of hydrophobic and hydrophilic moieties; therefore, surfactants show both lipophilic and hydrophilic properties (59, 60). The estimated annual world production of surfactants was at 15 million tons in 2005 (61). Besides the industrial (e.g., laundry detergents and cleaning supplies, detergents in cosmetics, and engine oil additives) and domestic (e.g., domestic laundry and dishwashing detergents and soaps) application of various surfactants (summarized in **Table 1**), the use in VDs and PPPs represents a substantial sector, as well. Surfactants enhance the efficiency of formulations by increasing the water solubility, bioavailability and biological activity of the active ingredients (62, 63). Surfactants may be used to solubilize drugs through micellar dispersion in VDs (64), furthermore, are applied in feed additives applied in drinking water as stabilizers to prevent decomposition of the active ingredient(s) in the preparation (65). Various types of surfactants used in veterinary

TABLE 1 | Various types of surfactants used for general purpose.

Chemical name	Product name	Type	Producer/supplier	CAS number
Sodium dodecyl benzene sulfonate	Neopelex G-65	Anionic	Kao Chemicals	25155-30-0
Lauryl glucoside, sodium lauryl glucose carboxylate	Plantapon LGC	Anionic	The Soap Kitchen	383178-66-3, 110615-47-9
Sodium xylene sulfonate	Stepanate SXS-93	Anionic	Stepan	1300-72-7
Cetyl trimethyl ammonium chloride	Dehyquart A-CA	Cationic	BASF	112-02-7
Lauryl dimethyl betaine (quaternary ammonium compound)	Emulson AG CB 30	Amphoteric	Lamberti SpA	66455-29-6
n-Dodecyl-n,n-dimethyl-3-ammonio-1-propanesulfonate	Zwittergent 3-12	Amphoteric	Merck Millipore	14933-08-5
Alkyl polyglucoside (lauryl glucoside)	Kemgluko CLM	Non-ionic	KemCare	110615-47-9
Cocamide diethanolamine	Amidet B-112	Non-ionic	Kao Chemicals	68603-42-9
Octylphenol ethoxylate	Triton X-100	Non-ionic	Dow	9002-93-1

TABLE 2 | Various types of surfactants used in veterinary drugs or disinfectants.

Chemical name	Product name	Type	Producer/supplier	CAS number
Dioctyl sodium sulfosuccinate	Vedco Veterinary Surfactant	Anionic	Respa Pharmaceuticals Inc	577-11-7
Didecyl dimethyl ammonium bromide	Bromosept 50	Cationic	ABIC Biological Laboratories Teva Ltd	2390-68-3
Alkyl dimethyl benzyl ammonium chloride (C_{12-18}) (ADBAC)	Dec-quat 100	Cationic	Veltek Associates Inc	68391-01-5
Alkyl dimethyl ethyl benzyl ammonium chloride (C_{12-14}) (ADBAC)				85409-23-0
Polyethylene glycol (PEG) glyceryl stearate	Gelucire 50/13 Gelucire 50/02	Non-ionic	Gattefossé SAS	9011-21-6
PEG glyceryl laurate	Gelucire 44/14	Non-ionic	Gattefossé SAS	57107-95-6
PEG-8 caprylic/capric glycerides	Labrasol	Non-ionic	Gattefossé SAS	61791-29-5
12-Hydroxystearic acid-polyethylene glycol copolymer	Solutol HS 15	Non-ionic	BASF	70142-34-6
Sorbitane ester ethoxylate	Polysorbate 80	Non-ionic	Croda Americas, Inc.	9005-65-6

TABLE 3 | Various types of surfactants used in feed additives.

Chemical name	Product name	Type	Producer/supplier	CAS number
Sodium lignosulfonate	Arbo S01P Borresperse Na	Anionic	KemTek Industries Inc Borregard Ligno Tech	8061-51-6
Calcium lignosulfonate	Borresperse Ca	Anionic	Borregard Ligno Tech	8061 52 7
Linear calcium dodecylbenzene sulfonate	Rhodacal 60/BE	Anionic	Solvay & Rhodia	26264-06-2
Glycerol-polyethylene glycol ricinoleate	Volamel Extra Alkamuls SC/242	Non-ionic	Nukamel Solvay & Rhodia	61791-12-6
Alcohols, C_{8-10}, ethoxylated propoxylated	Antarox BL 225	Non-ionic	Solvay & Rhodia	68603-25-8

medicine and in feed additives are summarized in **Tables 2** and **3**, respectively. In addition, surfactants or wetting agents enhance drug solubility and membrane permeability, prolong gastrointestinal residence time, and protect the active ingredient from luminal degradation and metabolism in the gut wall (66). Enhancement of bioavailability of polar compounds without affecting solubility characteristics can be achieved by absorption enhancers (e.g., anionic and non-ionic surfactants, acylamino acids, acylcarnitines, and lysolecithin) (67–69). Conversely, surfactants also applied to increase the *in vitro* solubility of lipophilic compounds (70, 71). Formulation is of particular importance for PPPs, as additives may aim not only to improve the solubility, adsorption, or penetration of the active ingredient in these formulations but also to enhance environmental stability, bioavailability, and capability to reach the site of action. Various types of surfactants used in pesticide formulations are summarized in **Table 4**. Surfactants are generally classified according to the type of their hydrophilic part; therefore, anionic, cationic, non-ionic, and amphoteric surfactants can be distinguished (72).

Anionic Surfactants

Various anionic surfactants, containing functional groups capable to dissociate to form anions as the polar part of the molecule [e.g., carbonates, sulfates, and most of all sulfonates, such as linear alkylbenzene sulfonates (LASs) and alkyl sulfonates], are frequently used in large quantities in VDs, feed additives, and PPPs. Anionic surfactants can enhance the biological efficacy of the active ingredient (73, 74) through direct binding to it (75) or modification of its adsorption. Moreover, they can act as enzyme activators or inhibitors by binding to the enzyme protein in a concentration-dependent manner and their binding affinity depends on the length of the alkyl chain in the surfactant (76). LASs can inhibit alkaline phosphatase and acid phosphatase enzymes (77), and sodium dodecyl sulfate (SDS) improves the intestinal absorption of active ingredients, e.g., the anthelmintic drug albendazole (78). Further surfactants, e.g., calcium dodecylbenzene sulfonate and lignosulfonate (e.g., Arbo), are used for the formulation of feed additives and PPPs. Perfluorinated sulfonates and carboxylic acids, including perfluorooctanoic acid and perfluorooctane

Chemical name	Product name	Type	Producer/supplier	CAS number
Alkyl (C_{8-10})-polyoxyethylene ether phosphate	Rolfen Bio	Anionic	Lamberti SpA	68130-47-2
POE alkyl phosphate ester				50769-39-6
Dioctyl sulfosuccinate sodium salt	Imbirol OT/NA/70	Anionic	Lamberti SpA	577-11-7
Sodium-alkyl polyglucoside citrate	Eucarol AGE-EC	Anionic	Lamberti SpA	151911-51-2
Sodium-alkyl polyglucoside sulfosuccinate (in aqueous solution)	Eucarol AGE 91/S K	Anionic	Lamberti SpA	151911-53-5
Sodium dodecyl benzene sulfonate	Agrosurf WP85	Anionic	Lankem Ltd	25155-30-0
Secondary alcohol ethoxylate	Tergitol 15-S-9	Non-ionic	Dow Chemicals	68131-40-8
POE (15) tallow amine formulated	Emulson AG GPE3/SSM	Non-ionic	Lamberti SpA	61791-26-2
Non-ylphenol polyethylene glycol ether	Triton N-57	Non-ionic	Dow	127087-87-0

sulfonate—suspected environmental endocrine disruptors—have been in use for over 50 years (79). Beyond agrochemical applications, the industrial use of several anionic surfactants, such as calcium dodecylbenzene sulfonate (Rhodacal 60/BE), sodium dodecylbenzene sulfonate (Neopelex G-65), ammonium lauryl sulfate (ALS), and sodium lauryl sulfate, in the formulations of laundry detergents and cleaning supplies is also significant (58, 72, 80). Sulfonates are among the most widely used anionic surfactants in personal care and household products (81, 82).

Cationic Surfactants

The polar part of cationic surfactants contains cation-forming functional groups. Among these, the representatives of primarily use are quaternary ammonium compounds (QACs), applied as disinfectants and cleaners, due to their advantageous adsorptive and bactericidal properties, in agricultural practice and veterinary medicine (83). The most commonly used QACs in veterinary and animal health practice are benzalkonium chloride (Bradophen), dialkyl dimethyl ammonium chlorides (ADBACs), and the so-called fourth generation of QACs, e.g., dioctyl dimethyl ammonium bromide and didecyl dimethyl ammonium bromide.

Non-Ionic Surfactants

In the molecular structure of non-ionic surfactants, a polyethylene glycol (PEG) moiety is connected to alkylphenols [i.e., alkylphenol ethoxylates (APEs), e.g., octylphenol (OP) and nonylphenol (NP) ethoxylates, suspected to exert hormone modulant effects; or long chain fatty alcohols, acids, or amines, e.g., alkylamine ethoxylates (ANEOs), polyethoxylated tallow amines (POEAs), fatty alcohol ethoxylates (AEOs), and fatty acid ethoxylates]. OP and NP derivatives are generally used in the production of non-ionic APEs (58, 84). In enterosolvent capsules used in veterinary medicine, water-miscible non-volatile and non-ionic surfactants are used for formulating poorly water-soluble compounds (85). Moreover, non-ionic surfactants are generally used as emulsifying or dispersing agents, emulsion stabilizers and binders in VDs, and feed additives (64). Non-ionic surfactants are generally applied as detergents in the industry and as formulating agents in PPPs (80). Additives for industrial use, such as cocamide monoethanolamine and diethanolamine (DEA), are used as foaming agents in different soaps, shampoos, and cosmetics, but despite their advantageous characteristics for industrial purposes, cocamide DEA has been classified to category 2B, possible human carcinogen, by

the International Agency for Research on Cancer (86). Alkyl polyglycosides (APGs), glyceryl laurate (e.g., monolaurin), and glycerol-polyethylene glycol ricinoleate (Volamel Extra) are often used as feed additives (e.g., emulsifier and stabilizer), due to their effect of increasing the digestibility of the animal feed (87). Polyethermethylsiloxanes, as trisiloxane surfactants, are often used in pesticide formulations to enhance the activity, efficiency, and the rain fastness of the active ingredient, due to their hydrophobic properties (88). Other surfactants for formulating PPPs include sodium alkylpolyglucoside citrate (Eucarol AGE-EC), POEA (Emulson AG GPE 3SS), and secondary AEOs (Tergitol 15-S-9) (89). A particular feature of OP ethoxylate (Triton X-100), as a non-ionic surfactant, is its capability for the lysis of integral membrane proteins; therefore, Triton X-100 is substantially used in biochemical studies (90, 91). Non-ionic surfactants are considered to exert lower toxicity than cationic, anionic, and amphoteric surfactants (59, 60). APGs are called "green surfactants" due to their low environmental impacts (92). However, the toxicity profile of tallow derivatives (e.g., POEA and hydrogenated tallow glycerides), used as surfactants in VDs and in PPPs as well, has recently become of significant importance in (eco)toxicological assessment (see "Tallow Derivatives" below).

Amphoteric Surfactants

Due to their zwitterionic structure, e.g., showing anionic and cationic characteristics simultaneously, amphoteric surfactants have high water solubility and show low contact toxicity characteristics, e.g., favorable dermatological and low eye irritation properties. In turn, amphoteric surfactants gained extensive use in cosmetics but are also widely used as adjuvants in agrochemicals. Their main groups are betaines, sultaines, iminodiacids, and acyl ethylene diamines (58, 80).

Biosurfactants

Natural surface-active substances are produced by plants, animals, and microorganisms (93). These biosurfactants, such as monoacylglycerols and their derivatives (e.g., ethoxylated monoglycerides, acetic, and diacetyl tartaric esters of monoglycerides) obtained from animal and plant lipids, including beef tallow, as well as rapeseed, lard, olive, and palm oils are widely used as emulsifiers in cosmetics, pharmaceutical industries, and foods (94–96). Additional biosurfactants used in veterinary preparations include wax and fat compounds (e.g., hydrogenated tallow, triglycerides, PEGs, fatty alcohols, fatty acids, or stearates) (64).

Several various anionic and neutral biosurfactants are known, but cationic biosurfactants have been described extremely rarely, probably due to their toxic effect (97). Generally, biosurfactants are considered biodegradable and relatively non-toxic (93). Biosurfactants, such as surface-active sophorolipids, assure surface-lowering properties, advantageous biodegradability, and low ecotoxicology, and are used in cosmetics, pharmaceuticals, and medical preparations due to their biological effects and activity (98).
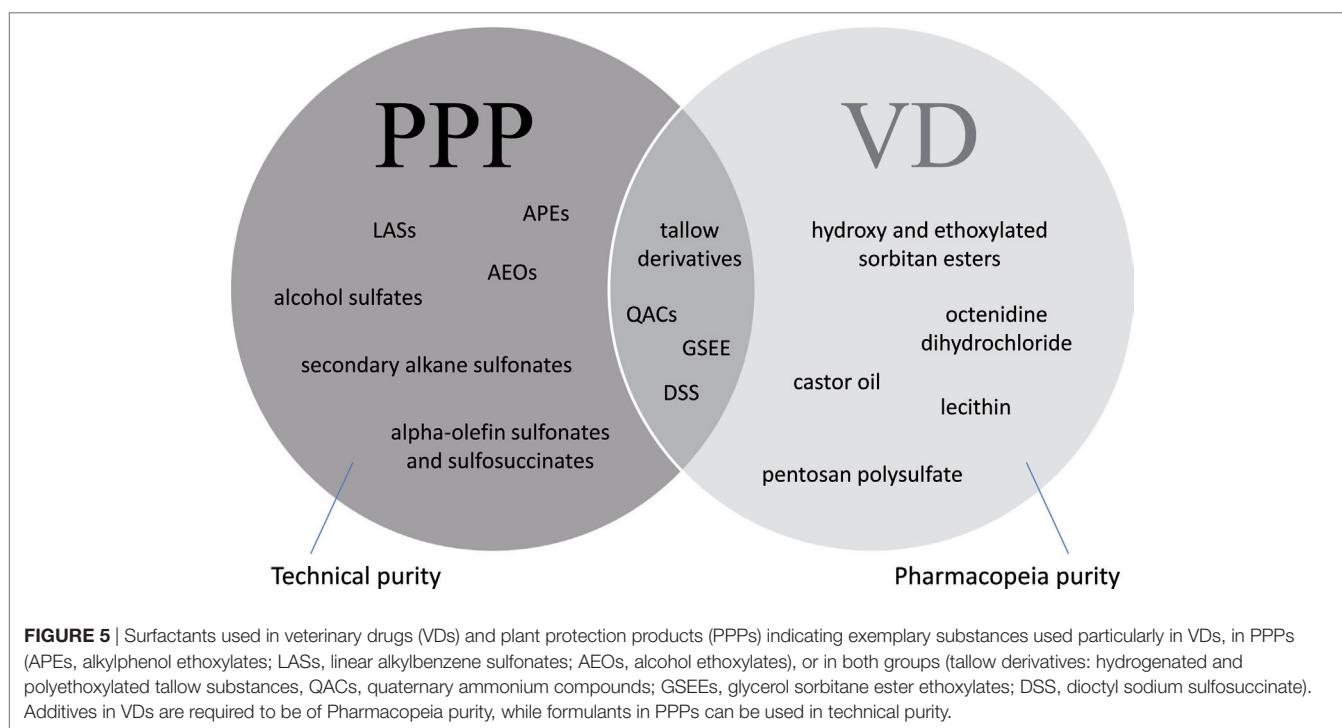
Tallow Derivatives

Generated wastes by the oil and fat industries, such as residual oils, lard, and tallow, are additional sources of cationic biosurfactants for fabric softeners. In addition, non-ionic tallow derivatives are used as surfactants in VDs and PPPs (99, 100). These substances are manufactured from biological resources via industrial chemical synthetic processes, therefore, are considered industrial chemicals. As seen above, surfactants derived from animal tallow, as non-ionic substances, have wide application in formulation of both veterinary products and PPPs. Yet, the biological origin cannot be considered as a guarantee for favorable toxicological characteristics, as indicated by several examples. Food, feed, and environmental safety of tallow have been assessed by EFSA (101) and EMA (102) only with regard to transmissible spongiform encephalopathy (TSE) infectivity. Despite possible TSE risk connected to tallow is considered by the Scientific Steering Committee of the EC, originated from protein impurities may be present in the final products (103), the EFSA scientific opinion document states that in general, the risk can be regarded as minimal on the basis of the calculated levels of exposure evaluated by quantitative risk analysis. The conditions

of the application of concerning animal by-products (e.g., tallow used as raw material for manufacturing tallow derivatives) are governed by Regulation (EC) No 1774/2002 (104). Upon being separated from animal fat via heat treatment (e.g., "fat melting"), moisture content reduction, and lipid separation, tallow is often subjected to chemical derivatization and corresponding tallow derivatives are occasionally also far from being unproblematic in their toxicity features, in spite of their long being considered as "inert ingredients" or "inert additives." The high toxicity of POEA, related to ANEOs, used primarily as a non-ionic formulating agent in glyphosate-based herbicides, was proven by several studies (105–108). POEA consists of a tallow amine moiety and two chains of repeating ethoxylate units. The tallow amine moiety is a mixture of amines derived from palmitic acid, stearic acid, oleic acid and other minor components (73). Non-ionic hydrogenated tallow glycerides are used as dispersing agents, emulsifying agents, emulsion stabilizers, and binders in VDs (64). Similarly, polyethoxylated mono- and diglycerides of tallow fatty acids are also listed in the corresponding EU lists of authorized substances.

Surfactant Usage in VDs and PPPs

Surfactants used in formulated VDs and PPPs may be characteristic to one or both of these product groups (**Figure 5**). Thus, certain substances, e.g., sorbitan esters and their ethoxylated derivatives, octenidine dihydrochloride, castor oil, pentosan polysulfate or lecithin are being used as excipients for VDs, but not for PPPs, while other compounds, e.g., APEs, LASs, AEOs, and alpha-olefin sulfonates and sulfosuccinates, are typically used for the formulation of PPPs. Certain substances, e.g., hydrogenated or polyethoxylated tallow derivatives, QACs or glycerol sorbitane

FIGURE 5 | Surfactants used in veterinary drugs (VDs) and plant protection products (PPPs) indicating exemplary substances used particularly in VDs, in PPPs (APEs, alkylphenol ethoxylates; LASs, linear alkylbenzene sulfonates; AEOs, alcohol ethoxylates), or in both groups (tallow derivatives: hydrogenated and polyethoxylated tallow substances, QACs, quaternary ammonium compounds; GSEEs, glycerol sorbitane ester ethoxylates; DSS, dioctyl sodium sulfosuccinate). Additives in VDs are required to be of Pharmacopeia purity, while formulants in PPPs can be used in technical purity.

ester ethoxylates, and alkyl sulfosuccinate salts, e.g., dioctyl sodium sulfosuccinate, may be used both for VDs and PPPs; however, it has to be emphasized that their chemical moiety is not equivalent even in these cases, as additives in VDs have to meet Pharmacopeia purity requirement, while regulations of PPPs allow the use of these additives in technical purity.

In 1998, the estimated global use of major classes of surfactants was 1.77, 0.35, 0.32, and 0.30 million tons for LASs, AEOs, APEs, and alcohol sulfates (109). Moreover, the annual global production of synthetic surfactants was about 7.2 million tons (59) and 2.8 million tons for the most popular synthetic anionic LASs (110). In the USA alone, the quantity of produced surfactants was at 3.5 million tons in 1999 and 35% of these were bio-based (111). In 2000, the total consumption of secondary alkane sulfonates was at about 0.072 million tons in Western Europe, while the application of alpha-olefin sulfonates and sulfosuccinates were 0.006 and 0.009 million tons, respectively (112), while annual usage of detergents and softener products were 4.25 and 1.19 million tons, respectively (113). Unfortunately, no details are readily available regarding the proportion of surfactants used in VDs and PPPs within these global trade values, but practically all of the chemical classes mentioned earlier are represented in this segment as well with the corresponding registration requirements considered. Thus, consumable surfactants registered to be used in VDs include castor oil ethoxylates, sorbitan esters, and their ethoxylated derivatives, as well as lecithin. Nonetheless, substances of less uniform characteristics, e.g., hydrogenated and polyethoxylated tallow derivatives, can also be used. The reported global production of surfactants was 8.6 million tons in 2003 (114). In 2005, the estimated annual world production of surfactants was at 15 million tons (61). Production and global use of non-ionic surfactants are continuously growing (115). Anionic surfactants emerged as the largest segment of the surfactants market in 2014, responsible for more than 45% of the global market; moreover, the global market of surfactants reached 20.2 billion US$ (116, 117). In 2015, it was estimated to 30.65 billion US$ (118). The overall surfactant market has been showing a constant growth in the last years, with the USA, China, Western Europe, and Asia being responsible for the largest rate of surfactant consumption (119).

Ecotoxicological Effects of Surfactants

Additives used as surfactants in VDs, feed additives, or PPP formulations may have adverse effects on the environment and on non-target organisms. The cytotoxicity order of surfactants investigated on rabbit corneal epithelial cells was found to be cationic > anionic = amphoteric > non-ionic (120). Surfactants may influence the embryonic development and hormonal balance of vertebrates, mainly in aquatic habitats, and genotoxic effects have been indicated for several types of surfactants (121–125). Lewis and Supernant investigated the effects of three types of surfactants, anionic C11.8 LAS, cationic cetyl trimethyl ammonium chloride (CTAC), and non-ionic C_{14-15} alkyl ethoxylates (AEOs), on several aquatic invertebrates and fish species. The order of the toxicity level was found to be AEO > CTAC > LAS (126). Singh and co-workers investigated the effects of several surfactants on fish species. The toxicity order of the investigated surfactants was

cationic surfactants > anionic surfactants > non-ionic surfactants (127). Interestingly, the toxic effect of monoalkyl QAC surfactants was not proven to increase with the alkyl chain length in the molecules (128). Anionic LASs have been shown to be uptaken by fish from water via the gills rather than the skin. The concentration of LAS surfactants increases rapidly in the liver and other internal organs of fish juveniles (129). Bioaccumulation in the aquatic environment is higher than in the terrestrial environment in the case of LASs (130). Pavlic et al. investigated the effects of nine detergent ingredients on algae species. Non-ionic detergent (decyl polyglycoside) exerted higher toxicity than anionic (e.g., sodium lauryl ether sulfate and ALS) or amphoteric (alkylamidopropyl betaine and alkylamidoethyl-*N*-hydroxyethyl glycine) ones (131). Jurado and co-workers investigated the effects of three APGs of different polymerization rates and alkyl chains, and toxicity increased with the alkyl chain length (132). An opposite role of the alkyl chain length of AEOs in the acute toxicity on the water flea, *Daphnia magna*, has been found in several studies (133, 134). LAS detergents caused abnormalities in the development in several marine invertebrates (135). NPs and OPs, as biodegradation products of APEs, exert toxicity on freshwater and marine fish species (136) and induce estrogenic responses (137, 138). Given APEs, e.g., NP ethoxylate, are suspected environmental endocrine disruptors, exerting hormone modulant effects themselves or through their AP metabolite, mostly as estrogen agonists (139, 140) or androstane agonists (141). Thus, the estrogenic activity of APs was demonstrated both *in vitro* (142) and *in vivo* (143). At molecular level, APs are capable to bind to estrogen receptors in fish and mammals (144, 145) and to activate reporter genes regulating estrogen-responsive elements (146, 147). Moreover, in aquatic animals, APs are capable to interfere with steroid metabolism (148) and steroid hormone receptor activity (149). Antiandrogenic activity due to altering aromatase activity and impeding the function of aryl hydrocarbon receptors has also been detected (150). Moreover, possible enhancing effects of given active ingredients (e.g., atrazine) and NP on 7,12-dimethylbenz[a]anthracene-induced mammary tumor development in human c-Ha-ras proto-oncogene transgenic rats have been evidenced (151).

The toxic effect of additives in PPPs has been clearly demonstrated by several studies in which formulated pesticide products were proven to be more toxic than their active ingredient alone (106, 152). Recently, the investigation of the combined toxicity of the worldwide most used herbicide active ingredient glyphosate and surfactant POEA as its most common formulant received special attention, as scientific evidence indicated higher individual toxicity of the surfactant or combined synergistic effects between the active ingredient and surfactants. The effects of POEA and a glyphosate-based herbicide formulation (Roundup) on different test organism were compared by Chu and Tsui, and POEA proved to be more toxic (106). The acute toxicity of glyphosate, a glyphosate-based formulation, and the surfactant applied in given formulation on aquatic invertebrates and fish species were investigated by Folmar et al., and POEA was proven to be the most toxic component, compared to the effects of technical grade glyphosate and the investigated formulation (105). In a later study, ethoxylated adjuvants used in glyphosate-based formulations proved to

be nearly ten thousand times more toxic than the toxicity of the active ingredient (107). This finding has been reconfirmed in numerous additional studies (108, 153); moreover, several studies verified POEA as the most toxic component on *D. magna* as well (108, 154). The permeability of cell membranes can be affected by POEA, resulting in the enhancement of the absorption capacity of the biologically active agents, their cytotoxicity and effects on the cells inducing apoptosis or necrosis (155). On the basis of these findings, POEA as a formulating agent was proposed to the MSs to be excluded from glyphosate-based pesticide formulations in the EU in 2016 (156). The ban includes numerous PPP formulations, including Roundup Classic, Roundup Classic Plus, Roundup Forte, as well as numerous other products under trade names other than Roundup.

Combined Effects: Synergism, Additive Effect, and Antagonism

Interactions may occur between the active ingredients and additives used in formulated VDs, feed additives or pesticides. Due to their parallel presence in the given formulations, these substances may modify each other's effects, and their combined effects may be additive, synergistic, or antagonistic (157). Combined toxicity of active ingredients has been confirmed recently in several studies (158); furthermore, the individual toxicity of several additives was verified as well (106, 152, 159). The simultaneous application and presence of non-ionic amine oxide-based surfactants and anionic surfactants in formulations has been proven to result in synergistic effects between the surfactants (160, 161).

As a consequence of the above mentioned results, the assumption that additives used in formulations are inactive (inert) ingredients has been falsified is numerous cases and should be considered significantly questionable on the basis of the scientific evidence. Combined effects of various active ingredients and surfactants have been confirmed in veterinary medicine as well. Antagonistic effects between various bacteriostatic and bactericidal compounds and synergistic effects between antiseptic anionic tensides and other disinfectants (e.g., hexachlorophene) have been observed. Moreover, the dissociation, α-chymotryptic degradation, and enteral absorption of insulin hexamers are influenced by the combination of SDS and the cationic cetyl trimethyl ammonium bromide surfactants in pharmaceuticals (162).

Combined toxicity and synergistic effects between active ingredient and formulating agents used in formulation of PPPs; moreover, the individual toxicity of surfactants applied in formulations were proven by several studies (108, 152, 153, 163). Various PPPs used in chemical plant protection were proven to be more toxic than the corresponding active ingredient, especially to aquatic organisms (108, 152). The toxicological evaluation of surfactants and other ingredients is essential for proper and effective ERA of formulations used in veterinary and agricultural practice.

Environmental Fate of Surfactants

Little information is available regarding the environmental fate of adjuvants (e.g., surfactants) after the application in VDs and PPPs (72). As a result of the significant production and industrial, agricultural, and domestic use, surfactants, their metabolites, and decomposition products can easily enter into environmental matrices, including soil, sediment, surface water, and even drinking water (58, 164, 165). A significant source of pollution is chemical plant protection, and also inadequate or uncontrolled management and treatment of wastewater and sewage sludge. Among different groups of environmental endocrine disruptors, e.g., drinking water contaminants, pesticide residues, surfactants, and industrial pollutants are highlighted (166).

Surfactants may sorb directly onto the surface of the solid phase in soil and sediment, or may interact with sorbed surfactant molecules as well (167–169). The adsorption capacity of surfactants is highly dependent on their physico-chemical characteristics (170). Cationic surfactants adsorb strongly onto the particles of soil and sediment (171), and the order of adsorption rate and affinity of surfactants is cationic > non-ionic > anionic (60), with cationic and non-ionic surfactants showing much higher sorption on soil and sediment particles than anionic surfactants (e.g., LASs). The degradation of APEs is faster in water than in sediment (172), and their metabolites are degraded more easily under aerobic than under anaerobic conditions (112, 173). In contrast, fatty AEOs are equally degradable in aerobic and anaerobic environments (174). Most of the surfactants can be degraded by microorganisms; however, various surfactants, such as LAS, dehydrogenated tallow dimethyl ammonium chloride, and APG, show environmental persistence under anaerobic conditions (60, 175). Surfactants bound to the surface of soil or sediment particles (e.g., POEA) can be directly taken up by the filter-feeding aquatic invertebrates [e.g., water fleas (*Cladocera*)], soil organisms [e.g., earthworms (*Lumbricidae*) and springtails (*Collembola*)], and thus, can enter into the food chain (176). Moreover, OP and NP compounds and their ethoxylates have been detected even in human breast milk (177) indicating substantive human exposure.

CONCLUSION

Residues of agrochemicals, e.g., VDs and PPP active ingredients, may reach food and feed products and through those can cause human, livestock, and environmental exposure. The rate of occurrence and the connectivity matrix of VDs and PPPs as contaminants in Europe are readily characterized by surveying notifications of contamination cases in the RASFF of the EU. Within such surveys, a comparative analysis of the numbers and trends in RASFF notifications for VDs and PPPs is rather informative. The identification cases of pesticide residues in the RASFF database are over 70% higher than that of VD residues: with 2,036 and 3,527 notifications for VDs and PPPs, respectively, between 2002 and 2016. Moreover, the two groups displayed opposing trends in time. Pesticide and VD residues rank 3rd and 7th in the overall notifications in RASFF, and the certainty in the RA status (obligatory to be assessed in RASFF since 2012) of the contamination cases is also more favorable for VDs than for pesticides. The initial high number of reported cases in 2002 for VD residues has successfully been pushed to a level below 100 cases annually by 2006. In contrast, the number of notification cases for pesticide

residues shows a gradual increase from a low (approximately 50 cases annually) initial level until 2005, with a drop only in 2016, still representing over 250 cases annually. These opposing tendencies are explained by differing toxicology background in the two sectors, the assessment of VDs being deeply rooted in the evaluation of human pharmaceuticals. Yet, the fact that most commonly found VD residues to date are antibiotics remains to be a substantial concern.

Network analysis of connections between notifying and consigning countries reveal a Germany–Vietnam axis with main notifier countries being Germany, Belgium, the UK, and Italy (63, 59, 42, and 31 notifications announced, respectively) and main consigning countries of extensive non-compliances being Vietnam, India, China, and Brazil (88, 50, 34, and 23 notifications received, respectively). Thus, countries of South and Southeast Asia are considered a vulnerable point with regard to VD residues entering the EU market.

Toxicity problems may emerge not only due to the active ingredients but also due to additives used for formulation of veterinary pharmaceuticals and pesticides. During the production of VDs, feed additives, and PPPs, significant amounts of different surfactants are applied. Surfactants in VDs are mainly used as disinfectants, surface cleaning supplies, agents for animal bath, emulsifying and dispersing agents, emulsion stabilizers, and binders. In feed additives surfactants promote better digestibility and availability of nutrients. In pesticide formulations, the efficiency of the applied active ingredient is enhanced by the use of surfactants as adjuvants. Additives used for the production of preparations applied as VDs, animal feed supplements and PPPs according to the current regulation, are considered as inert or inactive ingredients (13).

According to current legislation, simpler ERA of additives is sufficient than the requirements for the active ingredients. Regulatory requirements, health RA, and ERA of active ingredients used in VDs are very strict, similar to the legal requisites regarding human medicines. In case of pesticide formulations, full toxicology tests are required for the active ingredient(s), but not for the formulated preparation. The determination of MRLs for VDs includes all components used in the veterinary preparations and vaccines with pharmacological or pharmacodynamic activity (12). In contrast, MRLs are set for pesticide active ingredients and their metabolites only and not for their adjuvants (17). In addition, the quantity of acceptable daily intake (ADI-value) of different formulations is typically determined on the basis of studies conducted with the active ingredient and not with the formulated preparations (152).

Recently, additive, synergistic, or antagonistic effects between the active ingredient(s) and additives, as well as individual

toxicity of surfactants, have been demonstrated by several studies (106, 108, 152, 153). On the basis of the scientific evidence, the properties of these substances and their role in various biological interactions, these substances cannot be considered as unequivocally inactive ingredients by ecotoxicological and toxicological aspects in ERA of VDs, animal food supplements, and PPPs. Therefore, full toxicological assessment and evaluation of the adjuvants (e.g., surfactants) used in these formulated products is essential.

AUTHOR CONTRIBUTIONS

AS conceived the concept of the review. SK did the literature search, wrote the initial draft of the manuscript, and prepared the figures and tables. PB provided use and trade information, as well as physico-chemical data and descriptors of surfactants used in the formulation of VDs and PPPs. BD and AS oversaw the project, edited the manuscript, and took responsibility for the integrity of the data.

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The Potential for Big Data in Animal Disease Surveillance in Ireland

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INTRODUCTION

Animal Health Surveillance is the systematic collection, collation, analysis interpretation, and dissemination of animal health and welfare data from defined populations. This process is essentially about gathering intelligence to detect either novel animal health-related events or increases in animal health-related events as early as possible to better inform risk management at all levels within the industry (1). The incursion of an exotic disease, such as Foot and Mouth disease, is probably the most significant event from a national animal health perspective. The early detection of a newly emerging disease or the re-emergence of a disease which was previously eradicated from the state before it becomes widespread in the population is another important objective of a well functioning surveillance system. From a trade perspective, it is hugely important to demonstrate freedom from specific diseases, and this requires objective evidence upon which to base any declarations of freedom. While the presence of endemic diseases will be well established, there is a specific need to monitor the occurrence of endemic disease to identify any spikes in their occurrence and to take appropriate risk mitigation actions. Antimicrobial resistance (AMR) is emerging as one of the most significant public health concerns of the twenty-first century. The use of antimicrobials in livestock has come under increased scrutiny as a result. The monitoring of the use of the levels of antimicrobials in livestock and the emergence of resistance among animal pathogens are two important surveillance priorities in the years ahead. Animal health surveillance is a part of animal disease risk management in that the information garnered should lead to better informed risk mitigation strategies. These risk mitigation strategies must deal with risks that are well established as well as risks which are not yet fully understood, and therein lies the challenge.

DATA—NOT ALL DATA ARE EQUAL

Various data can be analyzed for surveillance purposes (**Figure 1**). However, the value of these sources cannot all be considered equal. Data acquired from postmortem examination from scanning surveillance is of a low volume but has a high resolution due to the detailed level of examination. This is followed in terms of precision by clinical examination by veterinary practitioners, where there is a larger volume of data, but it is considered less accurate than postmortem examination. Trends in mortality data, followed by trends in disease event recording are next in terms of data usefulness. Production data from herds and individual animals contains much more data points, with significant background noise interfering with the information. Data only becomes information when they are processed and these larger data sets need considerable data mining and analysis to make them into information which can be interpreted.
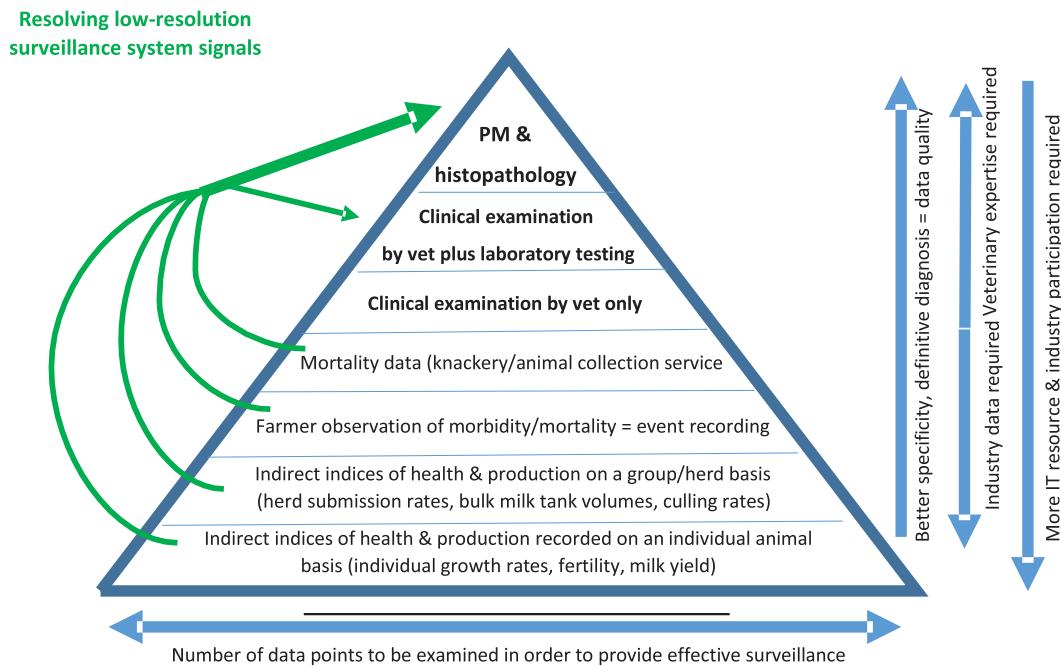
FIGURE 1 | The surveillance pyramid: quality vs width in animal disease surveillance.

CURRENT METHODS OF GATHERING SURVEILLANCE INFORMATION IN IRELAND

Currently, there is a network of six Regional Veterinary Laboratories in Ireland which gather passive surveillance data on submissions made by farmers on referral by their private veterinary practitioners. Submissions are made up of carcasses for postmortem examination and blood/feces samples for clinical pathology. However, the postmortem data are generally considered the more detailed and hence more valuable. An underutilized aspect of the current system is the soft intelligence created through conversations with private veterinary practitioners is not currently recorded nor analyzed. An analysis of telephone calls to Dutch animal health services in 2011, identified an increase in the prevalence of syndromes associated with the occurrence of Schmallenberg virus (SBV) in the weeks prior to the confirmed emergence of SBV (2). Serosurveys are carried out from time to time to gather information on the prevalence of diseases of particular interest. There are legislative requirements to survey various species annually to verify freedom from various diseases. These sampling frames have been used to carry out surveillance for other infections, such as SBV (3). Bulk milk antibody testing provides another method to get an insight into the health of dairy herds. Such serological testing tends to be of limited value where endemic disease has been established. Individual research projects are carried out from time to time on diseases of particular interest.

The Irish cattle industry is in the unique position of having its production database, which is operated by the Irish Cattle Breeding Federation (ICBF), directly linked to the Department of Agriculture, Food and the Marine's Animal Identity and Movement database. While the ICBF database's primary function relates to genetic and production data, these data could be used for animal health monitoring purposes. Similar databases in other countries have been successfully analyzed to find trends in mortality (4).

FUTURE OPPORTUNITIES

While there are vast volumes of data, which are not well integrated, integration could facilitate data mining and the use of data analytics to identify animal health-related risk earlier, so that those risks could be managed more efficiently. The costs of dealing with the animal health incidents at herd and national levels are disproportionately greater than the costs of carrying out comprehensive risk assessments using data analytics (5). An effective surveillance system will identify events sooner, and thereby allow corrective/preventive actions to take place sooner, and thereby limit the consequences of that event. However, in many countries, the availability of data and the analysis of those data is currently the limiting step. Data relating to weather, product price, and socioeconomic factors could also be integrated into such an approach. Modern milking systems have the ability to record yields per cow at each milking and such drops in milk yield has the potential to identify animal health at individual animal, herd, and regional levels.

Syndromic surveillance has been used in human public health policy to identify trends in public health. Databases relating to school and workplace absenteeism, General practitioner treatment records, Accident and Emergency treatment records and

over the counter medicine sales have provided syndromic data to be analyzed, looking for changes in demand patterns which can be linked to the health-related events in the general population. While there are no comparable data in veterinary medicine, there is potential to get information on diseases which are seen by veterinary practitioners but are not regulated by government. The emergence of AMR is directly related to the use of antimicrobials (6), and therefore, the monitoring of antimicrobial usage at individual farm level is an important element of control of AMR. Syndromic surveillance also offers an opportunity to monitor the actual usage of antimicrobials on farm, rather than sales. There is likely to be greater demand for such information in the future, to better inform the management of AMR.

The Irish dairy industry has embarked on a period of considerable expansion, as set out in Food Harvest 2020 and Foodwise 2025, two policy documents setting a strategic framework for the development of agriculture in Ireland (7, 8). In Ireland, we are fortunate to have large vast quantities of animal health-related data residing in national, veterinary practice and individual farm databases. While the techniques to interrogate these data for animal health risk management purposes have been developed elsewhere (9), their application in an Irish context has been limited to date.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and approved it for publication.

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frontiers
in Veterinary Science

Tapping the Vast Potential of the Data Deluge in Small-scale Food-Animal Production Businesses: Challenges to Near Real-time Data Analysis and Interpretation

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Food-animal production businesses are part of a data-driven ecosystem shaped by stringent requirements for traceability along the value chain and the expanding capabilities of connected products. Within this sector, the generation of animal health intelligence, in particular, in terms of antimicrobial usage, is hindered by the lack of a centralized framework for data storage and usage. In this Perspective, we delimit the 11 processes required for evidence-based decisions and explore processes 3 (digital data acquisition) to 10 (communication to decision-makers) in more depth. We argue that small agribusinesses disproportionally face challenges related to economies of scale given the high price of equipment and services. There are two main areas of concern regarding the collection and usage of digital farm data. First, recording platforms must be developed with the needs and constraints of small businesses in mind and move away from local data storage, which hinders data accessibility and interoperability. Second, such data are unstructured and exhibit properties that can prove challenging to its near real-time preprocessing and analysis in a sector that is largely lagging behind others in terms of computing infrastructure and buying into digital technologies. To complete the digital transformation of this sector, investment in rural digital infrastructure is required alongside the development of new business models to empower small businesses to commit to near real-time data capture. This approach will deliver critical information to fill gaps in our understanding of emerging diseases and antimicrobial resistance in production animals, eventually leading to effective evidence-based policies.

Keywords: antimicrobial usage, food-animal production, agribusiness, digitization, farm data

INTRODUCTION

The food-animal production sector, particularly in industrially developed countries, is evolving into a more data-driven ecosystem in which data are adding value not only to the business process but also to the entire food supply chain (1). This transformation is not only driven by technology but also by an increasing requirement for traceability and accountability initiated by regulatory frameworks (2), which can differ between countries, or directly by consumers (3). The use of antimicrobials in this sector, for both disease treatment and, in some countries, growth promotion, is

one of the areas directly affected by this evolution, with usage in livestock projected to increase by 67% by 2030 (4). Monitoring the volume of antimicrobial medicines used, and understanding under which conditions they are administered, are essential for identifying possible risk factors that could lead to the development and spread of antimicrobial resistance in animals. In many developing countries, these concepts are still at a very primitive level where one can still buy antibiotics without prescription. In fact, even in regions with clear guidelines on usage recording [e.g., in the EU, usage of critically important antimicrobials must be recorded (5)], a data gap persists (6). In many cases, this data gap does not result from the farmers failing to record the treatments they administer to their animals but from the fact that the data are often not digitized, nor centrally collected and are thus not amenable, or accessible for analysis in a way that allows decision-makers to utilize them.

In industrial countries, large food-animal production businesses have embraced digitization and manage their core business processes with enterprise resource planning, mediated by software and technology, in real-time. At the other end of the spectrum, small businesses, which tend to be made up of independent smallholders and family-operated businesses, are still faced with the challenges of storing, managing, and predominantly extracting value from the data they generate in a cost-effective manner. Revealing actionable animal health and business insights from data requires large mobilizations of technologies, infrastructure, and expertise, which are often too elaborate and costly for small-scale food-animal production businesses.

With increasing demand for animal protein for human consumption resulting in an increase in livestock number in low-/middle-income countries, coupled to a shift in production toward large-scale intensive practices in middle/high-income countries (7), data management, from the farm-level up, is increasingly pertinent in today's livestock value chain. We identified 11 processes taking place between the time a decision-maker, either farm- or office-based, formulates business questions and the moment they can take evidence-based decisions (**Figure 1**). In this Perspective paper, we explore processes 3 (digital data acquisition) to 10 (communication to decision-makers) in more depth, with a focus on the inherent challenges to the timely generation of animal health intelligence and how they disproportionally affect small-scale food-animal production businesses. While this perspective focuses on one particular type of agribusiness, food-animal production, many of the challenges and methodological solutions will also be applicable to other types and within other geopolitical jurisdictions.

DATA ACQUISITION AND STORAGE (PROCESSES 3–4)

The important question is not who captures the data, but how are they captured? Automated digital data capture increases data quality, by reducing bias in data entry, and volume while enabling the farmer to dedicate more time to animal care and maximizing returns. Today, a large proportion of agri-food data are collected through sensors and robots at all production
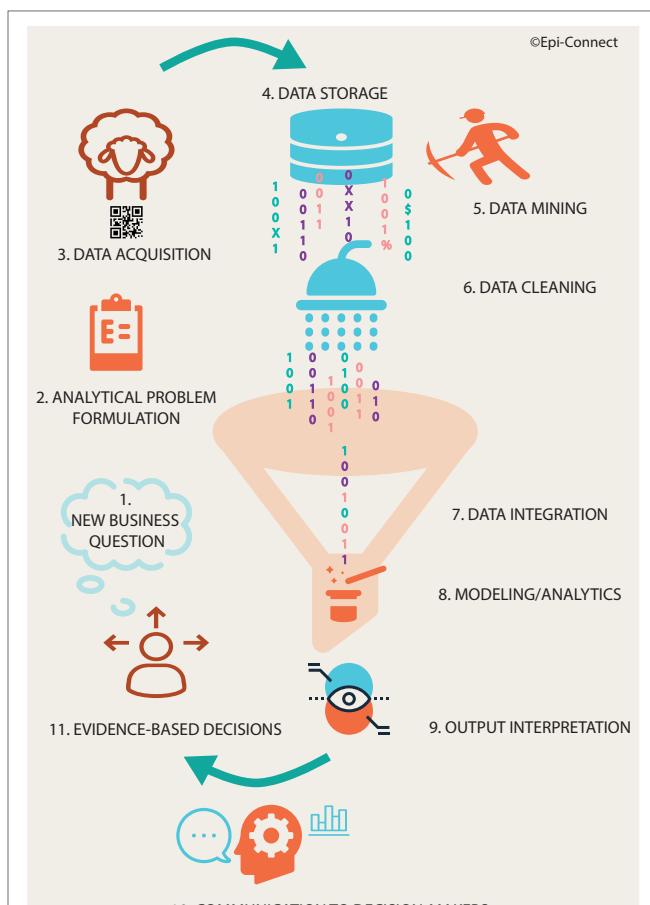

FIGURE 1 | Cycle of processes necessary to generate actionable animal health intelligence for decision-makers.

scales (8) (e.g., milking machines), often incorporated in the "Internet of Animal Health Things" (9), a network of objects that communicate with each other and with computers through the Internet. This automation of data collection raises issues about data governance and the companies that commercialize data recording products, for example, questions regarding data ownership, data access rights, and potential lock-in effects (e.g., a farmer not being able to migrate their historical data if they move to another supplier) (10).

However, animal health and drug usage data are seldom collected digitally in small businesses. One important contributing factor to this is the absence of a suitable recording platform (e.g., an App), which would offer user-friendly, dynamic, and editable real-time data acquisition. This does not mean that data on animal health and drug usage are scarce. To the contrary, these data exist often in the form of paper logbooks, but only a relatively small proportion of these data are readily automatable or exploitable. Missing metadata or ambiguous units of measurements, for example, contribute to the data being unfit for the derivation of intelligence. New recording platforms must be developed with the needs and constraints of small businesses in mind and must adhere to the FAIR data approach (11), i.e., capture data that are

- *F*indable (by both humans and computer systems),
- *A*ccessible (stored for long-term use; Open Access when possible),
- *I*nteroperable (see next section),
- *R*eusable.

Concerns about data security coupled to an often poor rural digital infrastructure (e.g., lack of access to reliable high-speed internet) result in many small businesses storing their data locally. This hinders data accessibility and interoperability as on-farm data storage capabilities may not be adequate to cope with the volume of data continuously being generated or may be weak in terms of security protocols (i.e., data corruption).

Furthermore, data on drug usage should not only be stored for compliance purposes but perhaps more importantly to generate animal health intelligence and herd management insights. To this end, increasing the size of the dataset used to generate such intelligence, by aggregating the data over several businesses, will add additional value to the data generated by each individual business. Farm data communities represent one way forward in the digital transformation of small businesses. These communities, such as Data Linker[1] in Australia/New Zealand, are increasingly being formed by farmers with a desire to take control over their data by choosing how they are shared in a way that may create opportunities for financial gains.

DATA MINING, CLEANSING, AND INTEGRATION (PROCESSES 5–7)

Farm data communities may receive the support of farm data aggregators. These aggregators leverage the active participation of the data communities in order to (a) aggregate their data for the derivation of actionable intelligence and/or (b) provide commercial services to other market stakeholders (e.g., feed companies) while ensuring maximum financial return to the businesses generating the data. However, both functions are not trivial as a large proportion of the data collected in agribusinesses is unstructured, i.e., it is text-heavy and seldom stored in relational databases. As such, it is necessary to preprocess the data by

- extracting from that large data pool, the data subset that is relevant to the business question asked (data mining);
- correcting, or removing, corrupt or inaccurate records and articulate the data subset(s) in a standard and structured form (data cleaning);
- combining data subsets residing in different sources to ultimately provide the users with a unified view (data integration).

Automated digital farm data exhibit properties (e.g., variety, and in some cases, volume and velocity), which can prove challenging to its near real-time preprocessing in a sector that is lagging behind others in terms of computing infrastructure and investments in digital technologies. To mine and clean data, the right technology needs to be in place to go through the volume of data and access the level of detail needed, all at high speed. This necessitates upgrading to more powerful hardware, turning to a grid computing approach, where machines are used in parallel to solve a problem more rapidly, or to a cloud computing approach.

Data interoperability between agribusinesses is still very poor, with the characteristically amorphous data typically lacking any binding information. It becomes necessary to apply semantic technology, such as control vocabularies (ontologies) and standards (e.g., agroXML[2]), to provide anchors to help interoperate and link across data. More specific information on the application of semantic technology to animal health data can be found in Ref. (12). Ideally, such a data annotation scheme would be built into the tools designed to capture the data, so that this is done automatically.

MODELING AND ANALYTICS (PROCESS 8)

Mere accumulation of data without any relevant output is both costly and useless. Data must provide timely and actionable animal health and business insights, and as such, careful plans regarding how the data will be analyzed and for what purpose must be made before the data acquisition stage. Modeling and analytics is about extracting important common features across many subpopulations even when large individual variation exists. The outputs from this process can be descriptive in nature; prescriptive (e.g., provide recommendations for improvement of a process); or predictive (13).

Digital data are characterized by high dimensionality (a lot of random variables) and large sample size features, which raise the following three analytical challenges (14). High dimensionality brings (1) noise (error) accumulation; (2) spurious correlations; and (3) incidental endogeneity (when many unrelated covariates incidentally correlate with the residual noises). High dimensionality combined with large sample size creates issues such as heavy computational cost and algorithmic instability (how a machine-learning algorithm is perturbed by small changes to its inputs). Finally, large samples aggregated from multiple sources at different time points using different technologies create issues with experimental variation (e.g., data collected under different and potentially non-comparable settings) and statistical biases (e.g., differences between an estimator's expected value and the true value of the parameter). Some of these challenges can be overcome through the development of more adaptive and robust statistical procedures; others rely on the analyst's ability to correctly infer based on the data and their limitations. The latter is particularly important in an era in which software such as Tableau[3] or IBM Watson[4] have "democratized" data modeling and visualization, allowing individuals without a background in data science to easily create data summary products (with the aim of deriving business intelligence) without a thorough understanding of statistics and inference (also see point below).

Methodological solutions exist for the reconciliation of data privacy concerns in respect to market competition and regulatory

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[1]http://www.datalinker.org.nz/.

[2]http://195.37.233.20/about/.
[3]https://www.tableau.com.
[4]https://www.ibm.com/watson/.

groups accessing the data with the release of sensitive data for analysis. For example, remote analysis infrastructures such as DataSHIELD[5] at Bristol University allow for pooled analyses without the need to access individual level data. Differential privacy addresses the paradox of maintaining individual anonymity, while increasing the understanding of a population (15) through the application of hashing (turning data into a unique string of random-looking characters), subsampling, and noise injection (adding random data to obscure sensitive personal information) techniques. Finally, data can be fed into complex statistical models to create synthetic data that are statistically identical (i.e., have the same statistical properties), but not an exact replica of the original data (16). Any query that can be asked of the original sensitive data can also be asked of the synthetic data, with the added benefit that the latter does not hold any personal information so that it cannot be traced back to any individual.

OUTPUT INTERPRETATION AND COMMUNICATION (PROCESSES 9–10)

Results from the data analysis and modeling stage need to be presented, verbally or visually, to decision-makers in a way that allow them to extract animal health intelligence. This process exemplifies the need for context. It is not enough for the quantitative analyst to be proficient with numbers; they must possess adequate domain expertise, i.e., an understanding of where the data come from, of the audience that will be consuming the analytical output, and how that audience will interpret these insights. There is a need to train more analysts with livestock and veterinary public health domain expertise: experts who can not only interpret the underlying statistics but also talk to the stakeholders in a way they can understand.

Data providers and knowledge users (if different entities) should put in place data use agreements, which clearly lay out the terms and conditions under which the knowledge derived from the data can be communicated and disseminated. Communication of any identifying or other sensitive information in an open forum can significantly damage a producer's livelihood and his/her reputation within the industry. With a strong data governance strategy in place, both negative and positive feedback to the data providers is to be encouraged in order to maintain or increase data quality, and hence data value, and ensure continued motivation and long-term data-driven business partnerships.

DISCUSSION

First and foremost, governments must provide or encourage (private) investments in rural digital infrastructure. Not only can these investments be expected to contribute to the resilience of rural communities, they will also help address policy challenges in a wide range of areas, including agriculture (17). For example, in the European Union, the new Animal Health Law [Regulation

(EU) 2016/429][6] stipulates that farmers "should therefore maintain up-to-date records of information which is relevant for assessing the animal health status, for traceability and for an epidemiological enquiry in the event of the occurrence of a listed disease. Those records should be easily accessible to the competent authority." While records in paper form are still legal (with the exception of some records, like animal identification, which must be electronic), the move is toward increasing the proportion of records kept digitally in the coming years. For mandatory data capture and submission, we argue that regulatory authorities have a duty to invest and develop safe data capture and storage protocols to maximize compliance and data quality.

The use of digital data products for animal health and business insights comes at a cost, albeit one which larger food-animal production businesses are able to afford with the anticipation of higher returns. Small businesses, however, face challenges related to economies of scale given the high price of equipment (e.g., for digital data capture or data storage) and services (e.g., data modeling and interpretation) related to data. So, how do we address this digital "power asymmetry" (18) between small and large agribusinesses?

One way to rebalance this power asymmetry could be through open-source data, and publicly funded analytical tools, for use in the public domain, which rival those of large agribusinesses in terms of complexity and innovation (18). Another solution could be to foster the use among small businesses of cloud computing technologies, i.e., buying information and communication technologies (ICT) as a service. Not only would this allow small agribusinesses to overcome some of the barriers associated with the high fixed costs of ICT investment (and its lock-in effect), it also allows them to switch more rapidly to newer/better technologies as the old ones become obsolete (17). We personally favor the latter and believe that the increasing number of small agribusinesses forming new, or joining existing farm data communities, as well as the advent of farm data aggregators provide the right conditions for this much-needed change in how ICT is done in this sector. Regardless of the choice of publicly funded analytical tools or buying ICT as a service, more should be done by knowledge users (e.g., regulatory authority or food standard scheme) to communicate to data producers (the agribusinesses) that data on their own, without the correct analysis and interpretation, are almost worthless. Data overload, in which enormous amount of data on animal monitoring and production are collected and left idle on a business' IT system, does not produce any intelligence, which can aid decision-maker unless it goes through the right pipeline (steps 5–10).

Perceived digital security risks may constitute a barrier to the adoption of these solutions. A secure digital agri-food chain is a shared responsibility as some risks will be displaced outside an agribusiness' span of control, highlighting the need for data governance strategies throughout the chain: what data are warehoused? Accessed? Analyzed? And by whom? These questions must be answered on a case-by-case basis, taking the needs and requirements of the businesses entering these data

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[5]http://research-information.bristol.ac.uk/en/projects/datashield(bfbb6ff5-8717-4085-a922-90795380d442).html.

[6]http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=OJ:L:2016:084:FULL&from=EN.

transactions. Attention must also be paid to questions of intellectual property. Ownership generally lies in who stores and controls the value of the data. However, isolated large datasets frequently hold little value; it is the combination of these data with that of quantitative analytics that creates the value (13), raising the questions of who owns the primary, secondary, or even the tertiary uses of the data? We feel that most people in the agri-sector do not hold the answers to these critical questions. Whether this is a result of the legal framework lagging behind the data revolution or a lack of transparency regarding the intellectual property, copyright and other ownership-like protections, small agribusinesses generating data fall under is unclear.

The animal health value chain has traditionally been a closed business ecosystem built on transactional relationships. This has resulted in knowledge being compartmentalized and in inefficient resource utilization. Today, this value chain is rapidly evolving with many new participants (e.g., feed companies, pharmaceutical companies) redefining the industry. Furthermore, the increasing capabilities of smart, connected products not only reshape competition within the industry but also expand the industry boundaries. As a result, we argue that new data-driven market and business models in the animal health industry must be developed in collaboration with all stakeholders along the food-animal production chain. These new business models should empower small-scale food-animal production businesses to commit and be rewarded for streamlined and near real-time digital data capture. This approach will deliver critical information to fill gaps that currently exist in our understanding of emerging diseases and antimicrobial resistance in production animals and will promote the accessibility of this valuable information to science and society, eventually leading to effective evidence-based policies.

AUTHOR CONTRIBUTIONS

Both FV and AT conceptualized and wrote this Perspective paper.

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Roadmap to the Digital Transformation of Animal Health Data

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THE CONTEXT

The use of antimicrobials in livestock production provides a basis to improve animal health and productivity which, in turn, contributes to food security, food safety, animal welfare, protection of livelihoods, and animal resources. However, there is increasing concern about levels of antimicrobial resistance in bacteria isolated from human, animal, food, and environmental samples and how this relates to the use of antimicrobials in livestock production.

The reality is that both the quantity and quality of data available on the usage of antimicrobials in livestock production is grossly inadequate. As a consequence, it is virtually impossible to assess the extent of overuse of antimicrobials in the treatment of livestock production. Equally, the pharmaceutical industry has little or no data on what percentage of the animal medicines, which are sold are actually administered, nor does it have any information in terms of treatment versus outcome.

Although government regulations in many countries require the recording of medicines administered to food producing animals, these are largely in the form of manually maintained drug records. Apart from the additional workload, which this imposes on farmers these data are not readily available for further analysis. In order to tackle the many challenges from antimicrobial resistance, it is essential to have real-time accurate data about antibiotic use in the treatment of animals.

The best solution would be to have such data captured at the point of treatment of the animal(s) and stored in a digital drug record. This would facilitate not only the sharing of such important data but would also enable further analysis for animal welfare and other purposes. This is possible using open global standards for the recording, storing, and sharing of such critical animal welfare data and should be an integral part of the animal traceability system.

WHAT ARE THE DRIVERS FOR THE MOVE TO DIGITAL, REAL-TIME DATA ON THE TREATMENT OF ANIMAL DISEASE?

- Public health—the need to tackle the increasing problems of health acquired infections caused by the prevalence of antibiotic resistant bacteria.
- Animal welfare—the need to treat animals with more appropriate levels of medication.
- Consumer trust—consumers need to have trust in the food supply chain, this is evident from the recent Horsegate scandal and the bovine spongiform encephalopathy outbreak.
- Sustainable agriculture—the need to reduce the impact of overuse of antibiotics on the soil and watercourses of farms.
- Provenance required by brands and retailers—as buyers, they are seeking to have greater assurance about the source of the food products, which they are selling to their customers.

- Technology—the Internet of Things (IOT) makes it possible to connect data on individual objects such as animals to systems for recording and reporting on their treatment and welfare.

HOW CAN DIGITIZED ANIMAL WELFARE RECORDS BE DELIVERED?

First, we need to start by using existing automatic data capture standards provided by GS1 (**Figure 1**). These are already used by more than 1.3 million companies operating in the food and some 20 other industry sectors worldwide. Indeed, the veterinary pharmaceutical manufacturers already mark their products with GS1 2D barcodes, which contain the product ID, the batch number, and expiry date. This means that veterinary surgeons/farmers could scan and record details of the medication administered to each animal.

Second, these data need to be stored in an animal's health record, again, there are global standards already in place for human health records (HL7), which could form the basis of an animal health record standard.

Third, data on animals/batches of animals could be shared between trusted parties across the food supply chain using the IOT. GS1's open standard—the Electronic Product Code Information System (EPCIS) enables this.

As for animal health records, capturing details of medication at point of administration to an animal would ensure greater accuracy of its health record. This also means that analysis can be carried out to compare treatment versus outcome, and this will not only help to improve medication regimes but will also provide invaluable data for other stakeholders, especially the veterinary pharma sector. In order to ensure interoperability of information and communication technology (ICT) systems and solutions, it is essential that a global standard is used for recording medication and disease data, given that HL7 already exists for this purpose for human health records, it seems obvious that this would be the most suitable solution to adopt.

This exact approach was very successfully implemented in the treatment of Irish hemophilia patients resulting not only in a complete traceability solution but significant improvement in terms of patient safety. The solution is centered on an electronic patient record and uses a mobile phone app

FIGURE 1 | How GS1's global standards work to move data between the various supply chain partners, thereby linking the physical flow of goods to the electronic data associated with them.

to scan all medication administered along with recording some clinical data. This real-time data collection enables clinicians to be proactive in the management of a patient's condition.

Similarly, a beef traceability solution was put in place covering the process from farm to fork, although initially designed to meet the batch traceability requirements of EC 1760 and the EU Food Law EC178, the updated system provides a one-to-one link between all primals produced from each animal. This means that if a customer has a complaint about an individual steak, then its provenance can immediately be checked back and any remedial action necessary can be taken. The system is based on the scanning of standardized labels placed on the primals, so when the retail butcher is preparing the meat for prepack or serve-over, the associated data are linked to the prepack label and ultimately to the customer's till receipt. A major German food retailer is using an EPCIS solution to provide customers with assurance on the traceability and sustainability of their meat and fish.

In conclusion, it is true to say that by leveraging the use of ICT and the IOT, it is eminently possible to make a transformational change to the way in which an animal's/batch of animals' medication history can be recorded and shared between trusted parties. Such a move can only help in the move toward more sustainable food production in compliance with the UN Sustainable Development Goals. Last, from the writer's experience, traceability solutions based on open

global standards invariably produce cost savings and real return on investment.

AUTHOR CONTRIBUTIONS

This manuscript was written by JB based on his knowledge of supply chain management and his considerable experience in the implementation of traceability solutions in the food, health care, and cosmetic sectors.

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BETTER POLICIES FOR BETTER LIVES

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frontiers
in Veterinary Science

Functionality and Interfaces of a Herd Health Decision Support System for Practising Dairy Cattle Veterinarians in New Zealand

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Decision-making processes to assess and improve the health of dairy herds are often unstructured due to the complexity of interactions that exist between the health and productivity of the herd, for which there are no ready to hand solutions. Decisions made in the face of these complex herd health problems are often based on the experience and perceptions of what might be a quick or the easiest solution. To shift from this unstructured process to semistructured decision-making requires a more holistic understanding of potential health problems and access to herd productivity information and to analytical methods suitable for examining and evaluating such data. Technological advances in agriculture have made the development of such information technology systems both possible and relatively accessible to decision makers working with dairy herds (e.g., veterinarians). The timely access and appropriate analysis of herd productivity data provides the herd health advisor with the opportunity to track and benchmark the performance of dairy herds. Thus, a decision support system (DSS) will use best available evidence to guide the allocation of resources to specific, most promising herd health interventions. This article presents an example of a DSS-based on collection of data and algorithm of analysis.

Keywords: dairy, productivity, decision support systems, herd health, technology

INTRODUCTION

Over the past 30 years, the New Zealand dairy industry has expanded with increases in cow numbers (2 million to over 5 million) and in the average size of milking herds (135 to over 400 cows). Concurrently, there has been a decrease in the number of dairy herds from 15,816 in 1982–1983 to 11,970 in 2015–2016 (1). Growing commercialization has affected several aspects of dairy farming including the management of herd health and productivity. Larger herd size requires the existence of a continuous and detailed decision-making and problem-solving process. Therefore, an efficient decision support system (DSS) framework is critical to enhance the work of farm management and health advisors (e.g., veterinarians) with their decision-making abilities focused on optimization of herd health and productivity.

Investment of dairy farmer into the state-of-art equipment, tools and software products have made it possible to monitor a range of outcomes including milk production parameters (e.g., bulk tank milk and individual cow milk yields and quality or the temperature of harvested milk), management parameters (e.g., herd structure, pasture availability), and environmental parameters

(e.g., environmental temperature and rainfall) (2, 3). These technological advances have improved the ability of herd managers to recognize deviations of heard production parameters from the norm and to implement timely corrective interventions.

Assessment and decision-making processes about herd health are often unstructured due to the complexity of interactions and the lack of immediate solutions to health problems facing the herd. In the face of these complex herd problems, decisions made by busy veterinarians tend to be based on experience, trial and error, and ease of implementation. For example, a sudden increase in a herd's bulk tank milk somatic cell count above the threshold set by the industry (400,000 cells/mL, New Zealand) downgrades the milk quality of that herd and could result in the dairy processor imposing significant financial penalties. This sudden change in milk quality is an indicator of an active mastitis outbreak in the milking herd. Farm management reacts by screening the milking herd to identify poor milk cows with poor milk quality and divert their milk from the milk supply.

A mastitis outbreak signals a potential flaw in the herd management's mastitis quality control process. The outbreak might be caused by a shift in the proportion of cows "at risk" for mastitis, higher than normal exposure to mastitis causing pathogens, improper milking routine, process failure in mastitis prevention protocols, or a combination of these factors. Screening and isolating cows with high somatic cell counts (poor milk quality) is an example of the unstructured approach to decision-making, which only aims to temporarily contain the effect of the outbreak on milk quality and economic return. The creation of a structured, or a semi-structured, decision-making process to contain this outbreak requires a better understanding, monitoring, and evaluation of the different components of the herds' health that could be influencing the risk of the outbreak. This in turn requires farm management to precisely define the set of relevant cow-level and herd-level milk quality information and to access any animal health database systems potentially critical to the decision-making process (4, 5). Milk quality and herd health information systems do exist, either on farm or online. However, accessing the appropriate information and deciding on the analytical methods to be used to derive an informed decision can be an overwhelming and challenging task for dairy veterinarian. An interactive and adaptable animal health DSS can help a dairy veterinarian in such decision-making. It should include analytical approaches appropriate for the identification of animal health problems and provide a range of solution options so that decision makers can effectively complete their decision-making processes and be able to predict consequences of interventions (4, 6).

In the context of the health of the herd, a well-designed DSS can be used to collect, store, and manage data. The data can be used for a number of purposes including descriptive and analytical epidemiological analyses. An effective DSS should have two main goals. The first goal is to provide herd health advisors with the ability to track both animal health and production performance. This is an essential requirement if farm managers and their advisors are to bench mark their herds against local and national herds. The second goal is to provide means to facilitate the identification of both the re-emergence of previous problems and development of new herd health problems. Prompt identification

of a new or recurrent problem allows immediate and appropriate actions to deal with issues and to efficiently allocate the resources necessary to mitigate the negative impact of such a problem during subsequent production periods. A well-designed DSS system uses the best available evidence to develop interventions aimed at improving the herd health and productivity and supports the design of ongoing disease surveillance strategies.
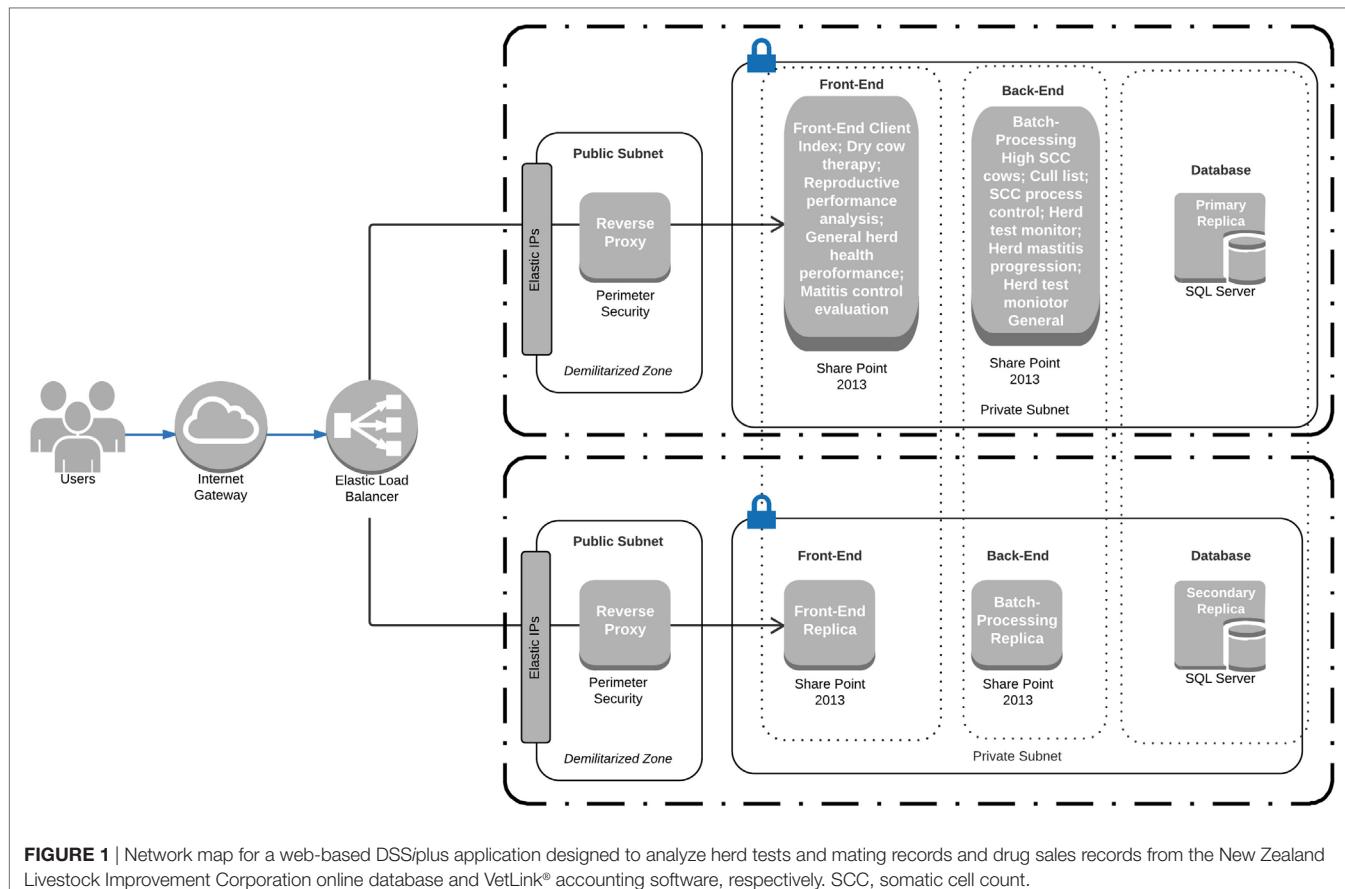
In New Zealand, as a part of the quality assurance program of a dairy herd, the milk processors (dairy milk companies) record the milk quantity and quality (bulk tank milk somatic cell count and bulk milk fat and protein percentages) for each bulk milk collection. The Livestock Improvement Corporation (LIC), the main dairy farming co-operative that serves approximately 80% of dairy farms in New Zealand, holds information regarding the genetics of member herds. These data include individual cow milk quality (individual cow milk somatic cell count, milk fat and protein percentages, and production index), insemination records, pregnancy diagnosis records, and reproduction index data. Dairy farmers and their advisors can access this information to assist in making informed decisions with respect to the routine management of their herds.

A number of DSS exist (e.g., ALPRO™ herd management system, DeLaval Limited, Hamilton New Zealand; DairyMGT™, University of Wisconsin-Madison, USA) that are either for commercial use or time consuming for busy clinicians. Currently, reviewing and comparing available DSS is beyond the scope of this article. In this short paper, we outline the conceptual framework, the functionality and interfaces for an in-house, web-based herd health DSS designed for a large veterinary practice (number of veterinarians using the DSS = 8) in New Zealand (DSS*i*plus). DSS*i*plus was designed for veterinary advisors and was used to transform milk and reproductive performance data and accounting transaction records into useful information at low cost. The information is critical for evidence-based, herd health decision-making, evaluation of implanted herd health-focused interventions and herd benchmarking.

Web-Based Herd Health Decision Support System: Concept and Methodology

Veterinarians are expected to assist farmers making complex decisions regarding maintaining good genetics of the herd and in the evaluation of the efficacy of mastitis and reproductive management strategies in the herd. The decisions are based on cows' historic health records (e.g., clinical mastitis events or amount and type antibiotic use on farm) and reproductive events (e.g., insemination records). A careful evaluation of the efficacy of the herd mastitis and reproductive management strategies (e.g., dry cow therapy, hormonal synchronization technologies, heat detection methods, or both) used in the herd allow farm management to formulate decisions specific to the herd.

Figure 1 shows a network map for a web-based DSS*i*plus application designed to analyze cow-level and herd-level milk quantity and quality data, reproductive (insemination) events (LIC's online database), and drug sales records (VetLink® accounting software, Vetlinksql, Takapuna, Auckland, New Zealand) for a veterinary practice located on the North Island of

FIGURE 1 | Network map for a web-based DSS*i*plus application designed to analyze herd tests and mating records and drug sales records from the New Zealand Livestock Improvement Corporation online database and VetLink® accounting software, respectively. SCC, somatic cell count.

New Zealand. On a daily basis, DSS*i*plus automatically acquired milk production, milk quality, and reproductive events data from two online database systems along with data from the in-house accounting software system.

Of-the-shelf, task automation software packages designed to perform automated tasks such as downloading data from online database systems are becoming more user friendly and more readily available. Open access statistical software packages are also available online. DSS*i*plus automatically acquires the data and then performs analyses of these data using open access statistical software ("*R*") (7). Using R's integrated suite of software packages facilitated all of the system's data acquisition, data manipulation, and data analyses.

Once the data were retrieved, outlier detection techniques remove outlier records and subject the cleaned data to various descriptive, analytical, and benchmarking analyses. For example, to assess the efficacy of a mastitis control program on a farm, quality control techniques (Shewhart charts) (8) were used to monitor somatic cell counts of bulk tank milk (adjusted for milk volume), identify unusual trends in the milk quality of dairy herds and to monitor mastitis control programs using lactating and dry cow therapy product sales as a proxy (**Figure 2**). DSS*i*plus utilized a series of descriptive and analytical data analyses techniques. Descriptive analyses (measures of central tendencies, measures of spread and frequency histograms) were used to visually

inspect somatic cell count as a function of calendar day and milk volume. Analytical techniques (e.g., mixed effects modeling and smoothing splines implemented within *R*) were used to identify and remove outlier values, to implement Shewhart quality control techniques, and to benchmark herds based on the reproductive performance.

DSS*i*plus also utilized log-log plots to analyze individual cow milk somatic cell count data as a means to characterize the efficiency of the mastitis treatment (lactating and dry cow therapy) and prevention (dry cow therapy) strategies used in the herd. The analyses track changes in udder health or mastitis severity through the lactation period. Crude statistical models were developed to estimate the number of clinical mastitis cases in a given herd based on the quantity of lactating and dry cow mastitis products sold to the client. This modeling process maximizes the utility of the accounting software by providing useful information for clinical decision-making. This procedure has allowed clients to be benchmarked as well as providing the opportunity to set goals for the next production season. Similar modeling techniques were used to analyze and benchmark client herds based on the herd's reproductive performance (**Figure 3**). This process involved the identification of weaknesses in specific areas of the current operation of a client's herd (calving interval, breeding program, animal health issues) that may be addressed to improve herd reproductive performance.
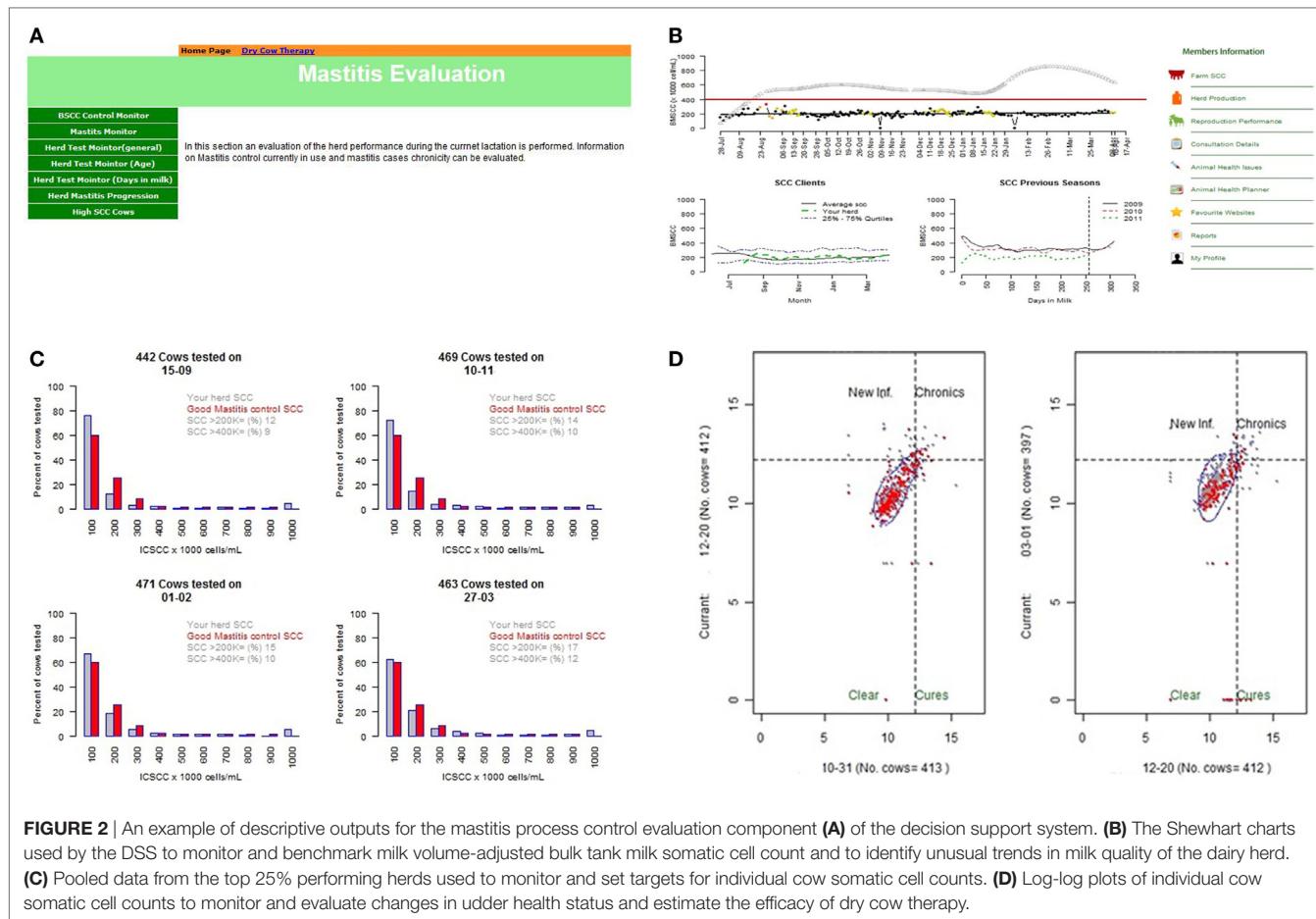
FIGURE 2 | An example of descriptive outputs for the mastitis process control evaluation component **(A)** of the decision support system. **(B)** The Shewhart charts used by the DSS to monitor and benchmark milk volume-adjusted bulk tank milk somatic cell count and to identify unusual trends in milk quality of the dairy herd. **(C)** Pooled data from the top 25% performing herds used to monitor and set targets for individual cow somatic cell counts. **(D)** Log-log plots of individual cow somatic cell counts to monitor and evaluate changes in udder health status and estimate the efficacy of dry cow therapy.

DSSiplus Functionality and Interface Challenges

The main functionality, interface challenges that were identified in the development of the DSSiplus concept framework included data ownership, data acquisition and processing, and integration of DSS*i*plus with existing information systems currently used by veterinary advisors and choosing where to set the performance targets of a herd.

Several data sets are generated for dairy herds. For example, milk quality, insemination, and reproductive data are supplied to farmers on a fee-for-service basis. Farm managers and their advisors can access these data through third-party online information systems managed by the data custodians (DairyNZ and LIC). Standardized functions and procedures [application programming interface (API)] that would allow veterinary advisors to create specific applications and subroutines to access features of the operating information do not exist. This lack of standardized API prevented efficient data acquisition and processing. Therefore, data acquisition and interface protocols had to be updated regularly to ensure a reliable streaming of data from the custodians of the data to the DSS.

Dairy farm operation management software systems (for mastitis and somatic cell count monitoring and reproductive management) or decision support systems rely heavily on the quality of farm records and the quality of the data retrieved from custodians of the online database systems. "Cleaning-up" of the data is an essential step before any descriptive and analytical analyses can be conducted. Unfortunately, the functional capacity of the information systems used by the data custodians does not go beyond simple record keeping summaries. The data outlier detection protocols used in the development phase of the DSS identified a number of anomalies in the row data that could influence the accuracy of the record keeping summaries accessible to farm management. These include, but were not limited to, extreme and biologically implausible records (particularly for milk quantity and quality) and duplicate animal-level records. Moreover, the herd is a dynamic population. Therefore, appropriate statistical techniques need be used to account for the herd's dynamic denominator data (i.e., the herd size at a given point in time) before any analytical procedures are applied on the data. Without appropriate data clean-up procedures and an accounting for the dynamic nature of the herd, simple summary statistics or measures of effect (e.g., proportions or rates) can be biased (overestimation or underestimation of effects) and imprecise. Bias reduction and enhancement of data precision are essential components of any system and critical to the transitioning from unstructured to structured, or semistructured, decision-making in dairy farm management (4, 5).
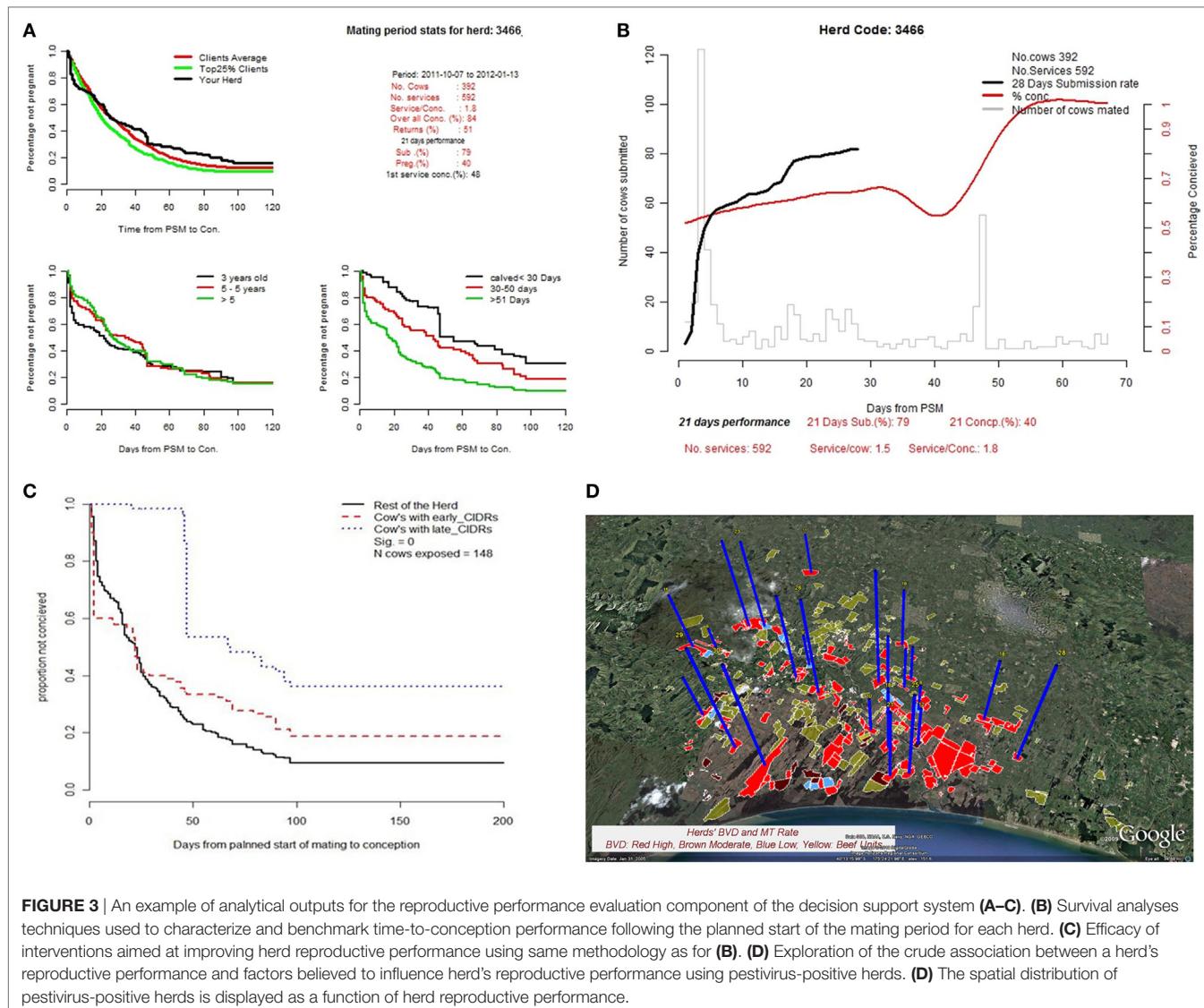
FIGURE 3 | An example of analytical outputs for the reproductive performance evaluation component of the decision support system **(A–C)**. **(B)** Survival analyses techniques used to characterize and benchmark time-to-conception performance following the planned start of the mating period for each herd. **(C)** Efficacy of interventions aimed at improving herd reproductive performance using same methodology as for **(B)**. **(D)** Exploration of the crude association between a herd's reproductive performance and factors believed to influence herd's reproductive performance using pestivirus-positive herds. **(D)** The spatial distribution of pestivirus-positive herds is displayed as a function of herd reproductive performance.

The concept of the performance targets underpins DSS*i*plus. Performance targets are created to optimize herd productivity in economic terms. The objective of the DSS is to define or monitor those targets that most closely relate to the economic efficiency of the herd (9, 10). A DSS should be able to benchmark the current reproductive performance of a herd (e.g., calving spread) or the somatic cell counts of bulk tank milk against that of previous production seasons and express the differences as a function of the herd's average milk production per lactation or the average milk production per cow.

Setting performance targets can be based on experience (using pooled client data) or on a review of the relevant literature. However, it is critical that the targets be set as herd targets and not as individual cow targets, since the foundation of the whole approach is based on treating the herd as the unit of performance.

Therefore, the first task in setting performance targets is to examine that particular aspect of the production process in detail and decide upon one or more productivity indicators

that will be used to represent a realistic economic target for the herd. An assumption inherent in this process is that achieving the productivity targets for the herd is synonymous with achieving the economic target. This is an essential first step in developing a DSS that will drive an evidence-based herd health program.

CONCLUSION

Dairy farm managers and their advisors have access to an array of underutilized data sources. At a low cost to dairy producers and their advisors, an in-house DSS is capable of automatically acquiring milk and herd performance data. Retrieved data can be interrogated using a variety of open access statistical packages to identify trends or explore significant associations in the data. The transformed information enhances the abilities of herd health advisors' to track and benchmark herd health and production performance against set performance targets and allows the

allocation of resources to interventions targeting herd health and productivity based on the best available evidence.

AUTHOR CONTRIBUTIONS

JA conducted the work described in this paper and wrote the manuscript. JH and TO contributed to the concept and application of the described work and edited the manuscript.

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The Future of Agriculture is Digital: Showcasting e-Estonia

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We live in digital society. This is evidenced by the extensive use of information technology in all spheres of life. Digital Society is not just a technology, but a comprehensive social organization, where the information and its exchange play a major role.

In this article, we present successes of Estonia's digital agenda and argue for coordinated farmer-centered actions for digitization of agriculture at the EU level.

MAIN PRINCIPLES OF e-ESTONIA

Conscious and systematic development of digital society is a strategic choice of Estonia since 1994. When Estonian political and technical leadership began laying the foundation for e-Estonia, it decided on certain principles:

- Decentralization. There's no central database, and every stakeholder, be it a government department, a ministry, or a business, gets to choose its own system in its own time.
- Interconnectivity. All the elements in the system have to be able to work together smoothly.
- Open platform. Any institution can use the public key infrastructure.
- Open-ended process. As a continuous project to keep growing and improving organically.

e-ESTONIA IS BASED ON X-ROAD AND e-ID

The two key ingredients in the infrastructure are the X-Road and e-Identity or e-ID. The mandatory national e-ID card serves as the digital access card for all of Estonia's e-services, including digital signature, while maintaining the highest level of security and trust.

The X-Road is a critical tool that connects all the decentralized components of the system together. It's the environment that allows the nation's various databases and registers, both in the public and private sector, to link up and operate in harmony, no matter what platform they use.

X-Road is the all-important connection between these databases, the tool that allows them to work together for maximum impact. All of the Estonian e-solutions that use multiple databases use X-Road. All outgoing data from the X-Road are digitally signed and encrypted. All incoming data are authenticated and logged.

Originally, X-Road was a system used for making queries to the different databases. Now, it has developed into a tool that can also write to multiple databases, transmit large data sets, and perform searches across several databases (1).

e-ESTONIA IN AGRICULTURE

Estonian farmers as all Estonian citizens benefit from the usage of e-services. According to a study on the impact of e-services in Estonia (2), users find that the e-services have helped them to save a lot of time, made communication with the government more accessible and easier and have

reduced possible errors. For example, time spent on applying for agricultural subsidies at Estonian Agricultural Registers and Information Board decreased from 300 min (filling in forms on paper) to 45 min by filling in an online application. Also, in Estonia, there have been no significant delays in paying out the subsidies. In general, users have saved the most time with e-services, which means that they no longer have to visit various government agencies nor obtain information from a previously separate information system.

Estonian farmers are keen to use new technologies, both in crop and animal husbandry sectors and the benefit of this usually do not raise any doubts. The most significant samples of digital agriculture in Estonia are following.

Geographical Information Applications

The Estonian public institutions have made serious efforts to develop the GIS systems. Thanks to the X-Road, all the systems are interconnectible and easily combinable *via application programming interface* (APIs). For example, as the databases of Estonian Land Board, E-Land Register, and Estonian Agricultural Registers and Information Board are interconnected, it is easy to find lots of information about any location in Estonian mainland, such as cadastral register number, intended land use, soil type, protected area restrictions, land owner, land user, etc. Unlike in many other countries, these data are open and accessible to public, as the trust and security is assured by access with e-ID. Additionally, the GPS technology enables to track the location and movement of tractors and other mobile machinery, so it is possible to gain full information about activities that are allowed and carried out in this location, also the level of productivity, etc.

Many of these data are practically used in operations of web and mobile applications that are developed for farm management, like VitalFields, eAgronom, Terake.eu. Using these apps has saved substantial amount of time for farmers from paperwork, as filling the fieldbook and compliance reporting for the payment agency are now automatized. Currently, developers focus to real-time data transfer from agricultural machinery into accounting without interim reporting. This would enable significant savings from data processing and more operative access to necessary information for farm management.

Livestock Performance Recording

In Estonia, the percentage of performance recording of dairy cattle is one of the highest in the world (95% in 2015), approaching rapidly to 100%. Performance recording enables access to data, which is necessary precondition for dairy farm management.

Estonian Livestock Performance Recording Ltd. (ELPR) has created very innovative applications for dairy farmers, which monitor dairy production, milk quality, and animal fertility indicators. Producers can input their data *via* web application, in particular, Vissuke for dairy, Possu for pigs (3). The databases of Livestock Performance Recording Ltd. are interconnected with Estonian Agricultural Registers and Information Board, which enables to synchronize the registration of changes in herd without doubling data entry and minimizes the possible errors. Most of Estonian producers use the ELPR database also for recording herd movement in the accountancy of their enterprises (4).

Project "Application of Performance Measurement System for More Informed Decision-Making and Increased Efficiency of Production Process at Dairy Farms"

Estonian University of Life Sciences and Estonian Animal Breeders Association have launched a joint project, whose aim is to create a possibility for managers and specialists of dairy farms for benchmarking efficiency of the production process. A special database is created for the project, where participating enterprises enter information about their expenditure and revenues, feed use, and herd movement. Data from ELPR databases are copied automatically in order to avoid double entries. On the basis of these data, the performance metrics (KPI's) are calculated, which serve as basis for the benchmarking.

One of the project's main keywords is promptness—data are collected monthly and feedback of the ongoing month's results is available within 2 months. The time lag compared to getting results from enterprise's own accountancy is only few weeks. Another significant novelty is the use of Qlik Sense, one of the leading Business Intelligence software packages for analyzing the results. Business Intelligence is highly topical in software development nowadays as it helps to process big data into applicable metrics and reports. Considering the amount of data and limited resources available for average agricultural enterprise, the use of Business Intelligence software might become highly important in the nearest future.

TECHNOLOGY ONLY IS NOT A SOLUTION, DATA ARE NOT AN INFORMATION

The use of technology combined with digital transformation can help farmers to achieve targets in increasing effectiveness and productivity, and to respond to dynamic markets. Nevertheless, the main question is, how to implement digital technologies, and use information produced in the farm management in a most efficient way. Paradoxically, while there are more and more data available to farmers, there are fewer and fewer resources (including management and workforce) to process these data, often because of tense economic and market situation. Solution could be provided by proper guidance and advisory services, but also by using DSS (*decision support systems*), which would liberate farmers from resource consuming data processing.

OPEN DATA, INTEROPERABILITY, AND STANDARDIZATION ARE CRUCIAL

A farm produces many types of data from diverse sources and format. When data are heterogeneous, it is frequently organized in data silos and ends up being separated from other data. Data silos can be created by private companies, public databases, or between states. For small countries like Estonia, avoiding generating data silos at the level of EU Member States is especially important in order to be competitive. Open data, interoperability, and standardization are crucial to avoid data silos. It is also vital to guarantee free access for farmers to public databases. In Estonia, there are well-developed interoperability and interconnectivity

between state level Geographic Information systems, but there is still a long way to go to fully open data (5). Interoperability between private companies mostly does not yet exist. For example, data produced in the tractor's computer are currently not accessible for third parties for using it in different applications as it is protected by license of tractor manufacturer. In case of change, the technology provider, it is impossible to transfer the previous data into new technology. Farmers should be granted appropriate and easy access and be able to retrieve their own data further down the line. They also should not be restricted should they wish to use their data in other systems. Access and data portability should be addressed at EU level, as the farmers, who are often SME-s, might easily be run over in the negotiations with big technology companies. Common understanding of data portability at EU level would also encourage independent software development besides of big technology companies, which would be more flexible and better meet farmers' needs.

DETAILS OF DATA OWNERSHIP MUST BE DISCUSSED FURTHER

Copa-Cogeca, the umbrella organization of EU farmers and agri-cooperatives, have stated that data produced on the farm or during farming operations should be owned by the farmers themselves (6). Farmers must have full control of the use of their personal and private data, also in case when private data can be identifiable in the further data processing. Ownership of aggregated data poses still many unanswered questions, like where exactly is the borderline between "raw" data from individual farm and the new knowledge processed with a specific methodology or algorithm? What to do in the situation when farmer would like to remove the data of his/her farm from the system? How to share the revenue obtained from the aggregated data between the original source (farmer) and the data processor company? These issues need to be discussed further in details with all the potentially interested parts, and common agreement would be favored, preferably at the EU level within the data sharing code of conduct, or coherent strategy of digitalization.

DIGITALIZATION SIMPLIFIES THE EU COMMON AGRICULTURAL POLICY

Apart from filling in the applications and reporting for agricultural subsidies online, an increased use of digitalization, remote sensing, and ICT would improve efficiency, quality, and timeliness of controls and audits. Nowadays, many indicators are precisely measurable and procedures can be automatized, so there

is no need to maintain the outdated CAP rules and controls just "for any case." The most time and resource consuming rules of the CAP should be found out and simplified *via* digital technologies. It would significantly reduce red tape and bureaucracy not only for farmers but also for administrators, both national and European, and every saved hour is a victory for our economy.

FARMERS ARE THE HEART OF DIGITALIZATION

Finally, it is crucial that farmers and agricultural sector are fully involved to all the discussions about digitalization, which are currently going on in EU and in the world. Launching the strategy and developing of EU common digital market involves many activities and initiatives, which can be useful for farming sector, like Digital Skills and Jobs Coalition Initiative (7). It is very important that the problems and questions mentioned above will be solved while considering the interests of farmers, not only from the point of view of the ICT sector or technology companies. Digitalization of farming sector would contribute to its competitiveness, help to raise farmers' income, and attract young people to join the traditional activity, which is vital for the whole society.

AUTHOR CONTRIBUTIONS

EK made substantial contribution to conception and acquisition of data, wrote the manuscript, checked the references, and acted as corresponding author.

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Conflict of Interest Statement: The author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Finding the Value in an Animal Health Data Economy: A Participatory Market Model Approach

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INTRODUCTION

It is accepted that the costs of a severe animal disease outbreak in a country or region leads to significant economic costs, at a minimum in the tens of millions of euro (1). Increasing policy oversight of animal health by governments to prevent such disease outbreaks has increased the activity and growth of the animal health industry. A recent report by Grand View Research estimates that the animal health market can be valued at over €30 billion annually, growing at over 5% per annum (2). Yet, there is mounting consumer pressure on food retailers and processors to reduce the amount of animal medicines suspected of entering the food chain. This pressure stems from fears of potential ill effects on human health of, for example, growth hormones or antibiotics consumed by humans without their knowledge through contaminated food products. Governments and retailers are responding through tighter regulation on medicines usage and higher standards of food production on farm (3). In Europe, the EU Commission is currently streamlining the oversight of animal health through a new Animal Health Law, under the SANTE directorate general.

The new law encourages the use of technology and promotes near real-time surveillance and monitoring of drug usage and disease. These measures are to be welcomed but now must be implemented by Member States. Even a cursory glance at animal health agencies displays many researchers, projects, collaborative initiatives, and competent authorities with often duplicated roles, responsibilities, and geography. These myriad efforts share some common deficiencies—lack of usage data and lack of timely data (4). An issue that the lack of timely usage data in generating concerns within the broad animal health industry including veterinary and public health research is antimicrobial resistance (AMR). The gap in knowledge of antibiotic sales versus antibiotic usage on farms for food producing animals is a source of frustration for many. While in the EU, inspection, auditing, and data collection processes are in place, the lack of digitized, transferable, near real-time data and information prevents the animal health industry from meeting the AMR challenge as effectively as possible.

With the almost ubiquitous nature of smartphones in farming now, there are many solutions on the market to enhance the digitization of important usage data. However, making these data available to researchers and policy makers has often been blocked by a misrepresentation of farmers' attitudes toward data ownership and a comfort with the *status quo* by agri-food and pharmaceutical industries. The most frequent roadblock erected in discussions around improved data capture and sharing is data ownership, specifically, "who owns the data?" This concept of "ownership" must be addressed, and we believe that emerging EU digital economy priorities enable a reframing of

data ownership. This reframing will force the entire animal health industry to create fresh market and business models to meet existing and emerging needs of farmers, researchers, policy makers, and consumers.

DATA TENSIONS IN THE ANIMAL HEALTH INDUSTRY

At the heart of this big data tension between farmers and animal health technology providers (AHTP) is the issue of intellectual property rights and "who owns and controls the data." In terms of ownership, the EU policy holds a clear delineation between data and information ownership; farmers own their farm data but when that raw data pass an inflection point where information is generated usually by an algorithm, there is a transition of data rights and ownership to the AHTP. From a farmer's perspective, this policy position raises concerns around: (i) data access—who can see my data? And how is my data being used? (ii) data portability—do I have the flexibility to share and reuse data across interoperable applications? (iii) price discrimination—will service providers who also have farm data, tailor their prescribed solution and pricing based on farm attributes to maximize their profits from the farmer? On the other side, the AHTPs also have data concerns around protecting the intellectual property rights of their algorithms from competitors, especially if the farmer wants to work with a different AHTP in the future. While farmers would argue that they need to receive a fair share of the value generated from their data, AHTPs would counter claim that no one farmer's data adds significant value to the margin, instead value is generated from their technical capability to aggregate data from many farms. However, given that there are only a limited number of farms in the EU (*circa* 10.8 million), the argument that autonomous animal health data of an individual farm has a near zero marginal value does not hold true. Moreover, the limited farm population base means that each customer acquisition has competitive consequences for AHTPs that adds real value to their profitability.

## OVERCOMING DATA TENSIONS: EVOLVING TO A PARTICIPATORY MARKET MODEL

Although an emerging market place, the current animal health data market model can be classified as a single-side data economic model (5) where farmers are considered homogenous and exchanges follow a linear path as AHTPs extract data, transform it, and sell output. This type of market model is often labeled as captive prescriptive and is characterized by a closed business system mentality where there is low collaboration between value chain actors but high farmer engagement. In this market model, the farmer is a passive stakeholder of an integrated animal health data value chain and adopts the role of franchiser/contractor with limited freedom.

However, the importance attributed to farm data in animal health places farmers in a new context and redefines their role in the value chain. Farmers are becoming more aware of the value

of their farm data and are moving from a passive value chain participant to becoming an integral, empowered, and participating stakeholder in the new data value chain. This participatory value chain adopts a network concept where actors collaborate to cocreate value that could not be created individually. In comparison to the traditional captive prescriptive market model, the complexity of this recharacterization of the animal health industry is significant as it will dramatically reshape the value model of the industry and the data-driven business models required by a participatory market model.

Figure 1 below presents our conceptualization of a Participatory Market model for the Animal Health Industry from a contextual and geographical representation and from a single actor perspective. In this model, the farmer is an active participant in the animal health data value chain. The farmer adopts the role of data controller and manages how their data is used and shared for economic interest. AHTPs must seek permission to use the data for defined purposes or to share data with other third parties or to combine with other data and so on. By becoming an active value chain participant, the farmer benefits through accessing the data market place and using data to both enhance productivity gains, reduce disease or reputational risks to the industry and to get revenue from the provided data. Outside the Animal Health Industry, there are some promising examples of technologies and companies that promote farmers retaining control of their data. Datalinker is a DairyNZ project that has established a set of protocols that enable secure, standardized data interchange between organizations controlled by farmer permissions and electronic license agreements. Another example is Farmobile, a company that sells a data collection tool that centralizes growers' agronomic data from multiple systems in one electronic farm record. Farmobile standardizes the data and makes it easily searchable for customers who want to purchase data and the farmers get 50% of the revenue derived from selling the data. These examples illustrate that to harness the data potential of individual farmers into useful quantities, aggregation is needed. What they also illustrate is that the participatory market place that is emerging resembles a platform business model where "*match-making*" intermediaries operate between AHTPs who need data as part of their value-added services and farmers who have adopted the role of data controller for economic benefit. In **Figure 1**, a new matchmaker role of a data farm aggregator (DFA) is foreseen in the animal health data value chain to act as an intermediator and facilitating agent between the Farmer and the AHTP market to exploit the active participation of the data farm community (DFC) to aggregate their data for the provision of commercial services to other market stakeholders while ensuring maximum value of the farmer's data. In essence, the DFA is a broker between the different actors and is responsible for acquiring data from farmers, aggregating it into a portfolio and offering animal health data to different market players. In return, the DFA receives the value it creates from these markets and shares it with the farmers as an incentive to engage in the data market.

It is also envisaged that the farmer will become part of a DFC, which can be considered from two perspectives. First, the farmer is part of a DFC because they are contracted to the same DFA but have no knowledge of one another and are free
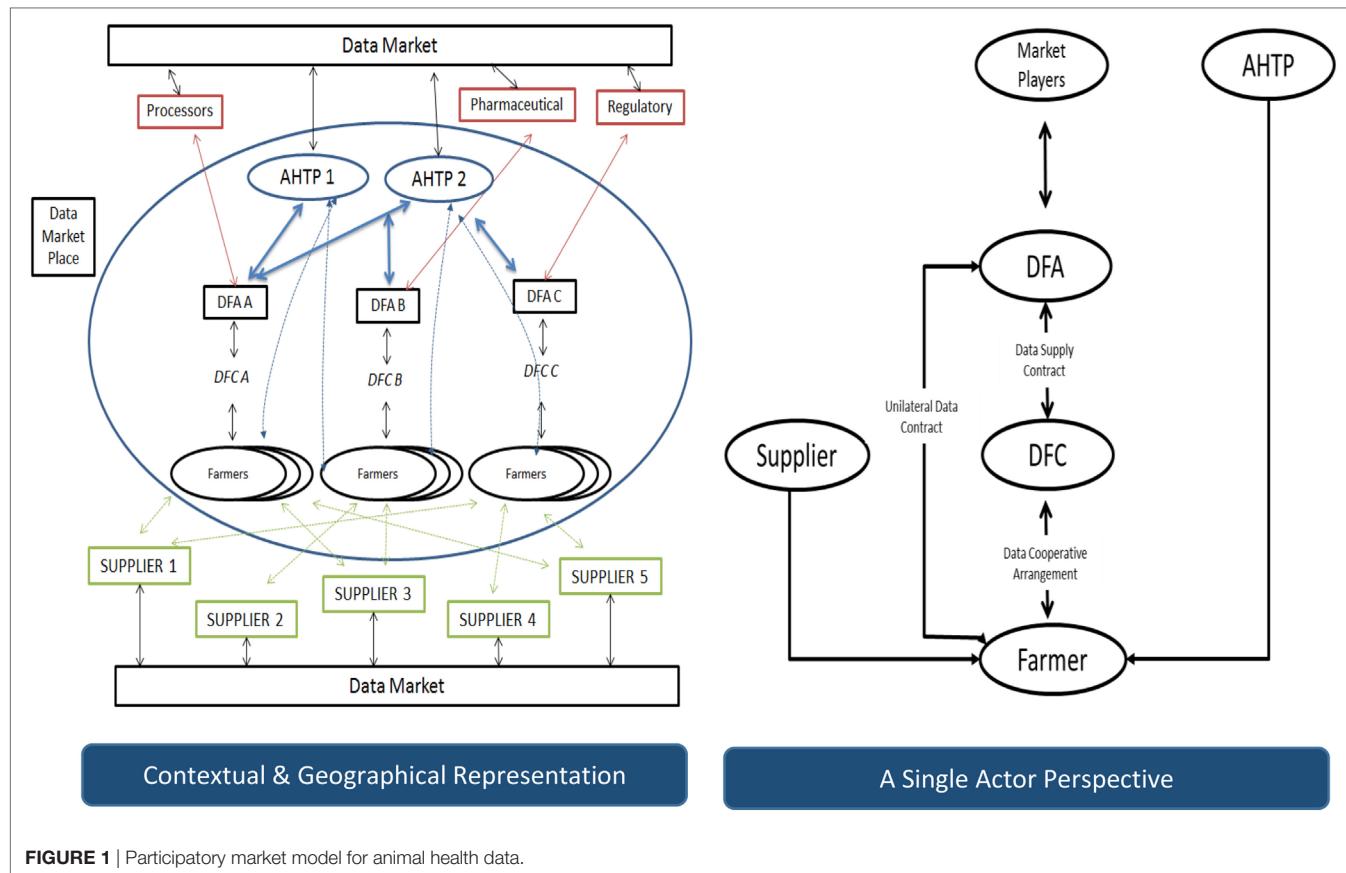
FIGURE 1 | Participatory market model for animal health data.

to choose the DFA that they prefer. Participation in the DFC enables trading of aggregated data between the farmers in the DFC through the DFA. In the second perspective, the DFC is a self-organized entity or cooperative where farmers are a member and collaborate to ensure maximum returns on their combined data value generated from their data supply and services. Examples of DFCs can be considered to exist in some veterinary practices as discussion groups or health focus groups emerge to discuss breeding, bio-security, or other best practice. As can be seen from **Figure 1**, more than one DFA can operate within a geographical area. This type of participatory market design is referred to as a two-sided or multi-sided economic model because it acts as a matchmaker between different value chain stakeholders. Revenue models will be complex as different data transactions are answered and settled for. There will also be multiple types of buyers and/or sellers and, in fact, a single party can be both a buyer and a seller of data.

CONCLUSION

Data is at the core of the emerging animal health market model landscape. Although embryonic and complex in nature, this new participatory market landscape holds significant new business opportunities. The emergence of the data farmer as a valid and integral value chain member means that companies must become more attuned to the needs of the farmer and design new

value propositions to attract and secure their data contracts. Indeed, an acute challenge of participatory business models is that a critical mass of farmers will be required to be attractive as a data intermediary to the marketplace. This means that the DFA must devote much attention to designing innovative business strategies to get on-board as many early adopters as possible to drive this network effect. Considering no current actor in the traditional animal health industry has a participatory or multi-side nature to their business model, the complexity of this recharacterization, especially for incumbents will be significant. To date, animal health market actors have tended to focus and rely on technology innovation as the driving force for the evolution of the industry and this is within their comfort circle; however, the data-driven nature of these technology advancements will also require a call to action to engage in business model transformation which is new to most. What is being put forward here is that sophisticated new participatory business models are needed to support near real-time surveillance and monitoring of drug usage and disease with the additional benefit of making quality datasets available for research to meet animal and public health priorities, such as AMR.

AUTHOR CONTRIBUTIONS

Sinead Quealy provided the agricultural and animal health industry perspective, examples, and knowledge. Patrick Lynch

applied his extensive work and expertise in market models and data-driven business models to the opportunities in agri-food and animal health industries to meet challenges in a shifting setting.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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