

# Veterinary pharmacovigilance in Europe: a survey of veterinary practitioners

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## ABSTRACT

A web-based survey was conducted by the Federation of Veterinarians of Europe with the support of the European Medicines Agency to gain a better insight into the adverse event reporting habits of veterinary practitioners and the level of information on reported adverse events that flows back to them. It was completed by 3545 veterinarians. The findings indicate marked under-reporting and that the system is poorly equipped to deal with lack of expected efficacy, with few cases reported and most found to be inconclusive. It was also found that feedback systems are greatly lacking. In order to increase spontaneous reporting, there is a need to make reporting easier (eg, by developing mobile apps, to incorporate the reporting into the practice management system software) and to make veterinarians better aware of the importance of reporting and the added value it may bring. Feedback systems should be improved. The best way to motivate reporters is to demonstrate that the reports they submit are indeed useful and contribute to the improved use of veterinary medicinal products. The major role veterinarians can play in improving animal health, welfare and public health by reporting adverse events needs to be further promoted.

## INTRODUCTION

An adverse event is an unfavourable or unintended observation in animals that occurs after recommended or off-label use of a veterinary medicinal product whether or not it is considered to be product-related. The definition also includes suspected lack of expected efficacy and noxious events in human beings after being exposed to veterinary medicinal products (VICH 2007).

Although extensive testing is carried out on the safety and efficacy of veterinary medicines before authorisation, information on adverse events that an animal or a user may experience is still relatively limited. Certain interactions as well as rare adverse events or events specific to certain breeds or groups of animals may only be identified when the product is used more widely.

Veterinary pharmacovigilance is the ongoing monitoring and evaluation of adverse events including lack of efficacy after use of veterinary

medicines to improve their safety and use. It is therefore important that all suspected adverse events are reported to enable continued monitoring and to take action where necessary to ensure that the benefits of the medicine outweigh the risks.

In the EU, legislation requires all adverse event reports following the use of authorised veterinary medicinal products to be collected and evaluated both by the marketing authorisation holder responsible for the product, by the national competent authorities (NCAs) and/or the European Medicines Agency (EMA) (EC 2001, EC 2011). Serious adverse events in animals and all human reports are collated in a single database, EudraVigilance Veterinary (EMA 2017). By the end of 2015, the EudraVigilance Veterinary database contained approximately 170 000 reports of adverse events, including 101 000 from the EU (EMA 2016c).

In many countries, veterinarians have a legal obligation to report adverse events. Nevertheless, reporting practices vary greatly between countries and between the species concerned (EMA 2015a). To our knowledge, no previous Europe-wide studies describe the adverse event reporting practices of veterinarians in Europe. Therefore, the Federation of Veterinarians of Europe (FVE) together with EMA designed a survey to gain an insight into the main challenges and obstacles for reporting adverse events and to examine how much information on adverse events reported flows back to them.

## MATERIALS AND METHODS

An electronic survey (SurveyMonkey) was drafted by the FVE and EMA, tested with a pilot audience comprising pharmacovigilance experts and practising veterinarians and translated into 22 languages. The online survey was open between 21 September 2015 and 31 December 2015. The survey was promoted to veterinarians across Europe through the FVE



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members and the members of the Committee for Medicinal Products for Veterinary Use Pharmacovigilance Working Party. FVE members, comprising 46 national veterinary associations from 38 European countries, promoted the survey through their communication channels such as websites, publications or dedicated journals. The survey was voluntary and anonymous, and participants were informed that their answers would be analysed for an EU report on pharmacovigilance. The survey comprised five sections (demography, observation of adverse events, off-label use, reporting and feedback) with a total of 19 questions, all of which were non-mandatory. Agreed definitions were included in the survey for clarity. The replies received were analysed by an independent data analysis company (Mirza & Nacey Research). Data were analysed for all responses (gross total), at the level of type of practitioners and by country, selected on the basis of receiving more than 50 responses. Descriptive statistical analysis was done using MS Access and MS Excel. The statistical validity of these results is accurate to within  $\pm 2$  per cent at the 95 per cent confidence level. The accuracy varies for each individual country.

## RESULTS

The survey was completed by 3545 veterinarians from 57 countries, of whom 3356 were from countries of the EU and European Free Trade Association (EFTA). With a target audience of approximately 108 000 practising veterinarians in the EU and EFTA (based on the FVE demographic report (FVE 2015)), this means that approximately 3.1 per cent responded. Fig 1 displays the EU/EFTA countries with more than 50 responses and one-third country namely Serbia. The greatest response came from veterinarians from France. The 'other countries' category — being countries with less than 50 responses — includes 341 responses and is not shown.

Approximately half (50.1 per cent) of the respondents worked in (mainly) companion animal practice, 24.3 per cent in mixed practice, 14.3 per cent in (mainly) food-producing animal practice, 4.8 per cent in equine practice and 6.5 per cent in other veterinary occupations (exotic or zoo animals, official veterinarians, academia or research, or working in the animal health industry).

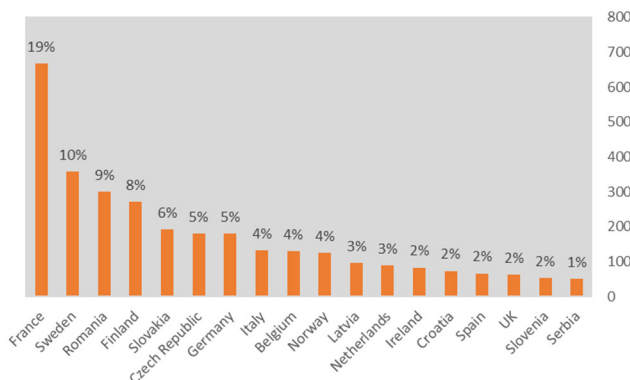


FIG 1: Which country are you from?

## Frequency of observing adverse events or lack of efficacy to a treatment

The majority of respondents (58 per cent; ie, 1788 of the 3079) reported that they rarely observed adverse events (in less than 1 per cent of the cases when they administered or prescribed a medicine), 32 per cent answered frequently (between 1 per cent and 5 per cent of the cases), 5 per cent very frequently (in more than 5 per cent of the cases) and another 5 per cent had not observed any adverse events. While companion animal veterinarians (7 per cent) replied they saw adverse events more frequently (answering 'frequently' or 'sometimes') than food-producing veterinarians (2 per cent), this difference could not be proven to be of statistical significance (Fig 2).

Small differences were seen between the countries, with the highest frequency of adverse events noted to be seen in Serbia (56 per cent of Serbian veterinarians answered very frequently, frequently or sometimes) and the least frequent adverse events noted to be seen in Ireland (79 per cent Irish veterinarians answered rarely).

Of the type of adverse events observed, non-serious events were most frequently seen (Fig 3). Serious adverse events were observed much less, with 67 per cent of respondents (1454/2181) saying they rarely saw serious events (less than 1 per cent of cases). Human adverse events were observed rarely, with 92 per cent of respondents saying they saw events in human beings in less than 1 per cent of cases (2404/2626).

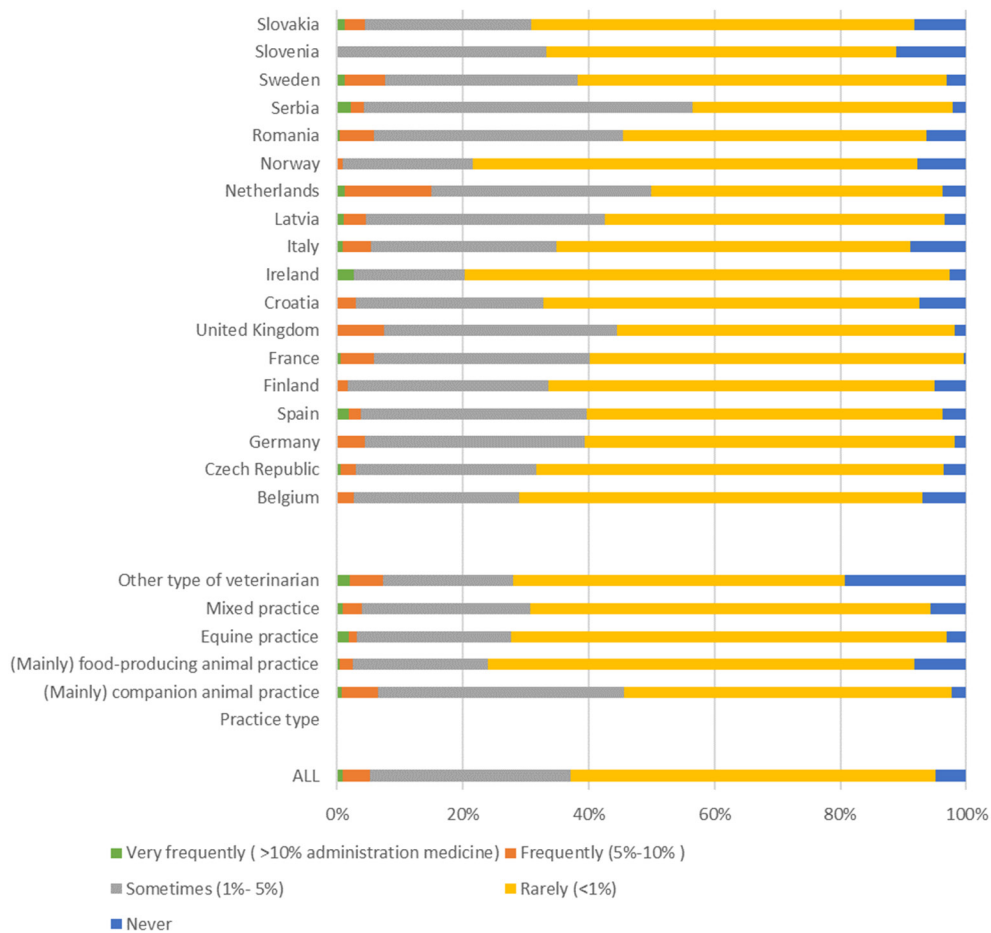
Respondents were asked how often they observe lack of expected efficacy. Forty-seven per cent (1363/2899) observed lack of expected efficacy sometimes (in 1–5 per cent of the occasions they administered a medicine), 37 per cent rarely (in less than one per cent of the cases), 12 per cent frequently (in more than 5 per cent of the cases) and 4 per cent never saw lack of efficacy. Little difference was seen between the different types of practice; however, differences were more pronounced between the different countries, with Serbia, UK, Romania and The Netherlands reporting having observed the greatest proportion of lack of expected efficacy and Slovakia the least (Fig 4).

Overall, it was noted with statistical significance that lack of expected efficacy was more frequently observed (11 per cent) than adverse events (6 per cent) (Fig 5).

## Reporting of adverse events

Forty-three per cent of the veterinarians reported at least one adverse event in the last year. Most reports (30 per cent) were for companion animals versus 13 per cent in food-producing animals. The majority of veterinarians (57 per cent) had not made any reports in the last year. Out of all companion animal veterinarians who made one or more reports in the last year, 92 per cent were adverse events reports and 8 per cent for lack of efficacy. With respect to food-producing animal reports, these were 93 per cent and 7 per cent, respectively.

Countries where veterinarians reported the greatest number of adverse events were the UK, France and Germany (58 per cent, 57 per cent and 43 per cent of



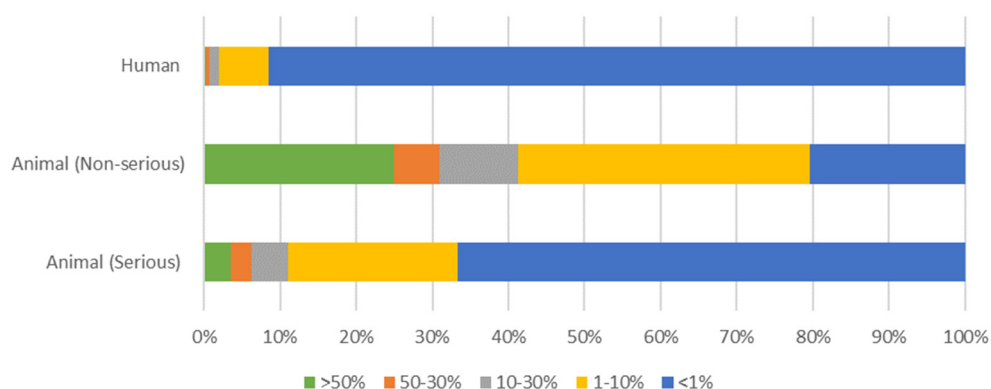
**FIG 2:** Frequency of seeing adverse events per country/practice type.

respondents, respectively, submitting more than one report over the last year). In all other countries, less than 30 per cent submitted a report, and in Romania and Latvia less than 10 per cent had reported.

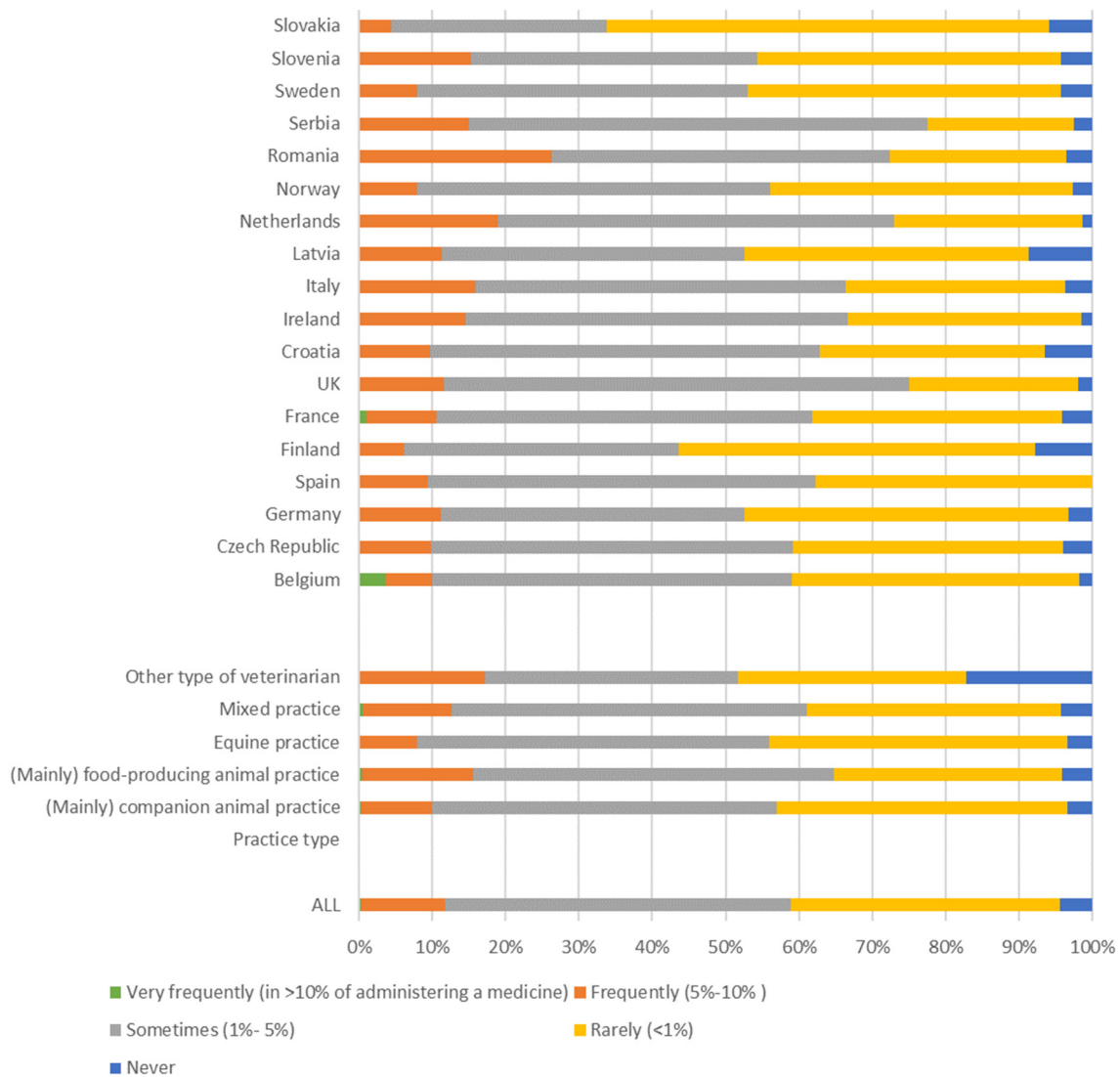
For food-producing animals, the greatest number of reporters was from The Netherlands (38 per cent of respondents said to have done more than one report in the last year). In all other countries, less than 20 per cent had reported an adverse event, and in Czech Republic, Croatia, Finland, Latvia, Norway, Romania, Slovenia, Spain and UK, less than 10 per cent had done a report.

### Off-label use

Of all respondents who provided information on off-label use ( $n=2975$ ), 45 per cent replied that between 1 per cent and 10 per cent of their prescriptions were off-label, 25 per cent reported more than 10 per cent, and 30 per cent less than 1 per cent. Between the types of practice, off-label use was seen mostly in equine practice and the least in mixed practice. Large variations were observed between the different countries, with off-label use most frequently reported in the UK and the least in Croatia.



**FIG 3:** Frequency of type of adverse events observed.



**FIG 4:** Frequency of observing lack of efficacy per country/practice type.

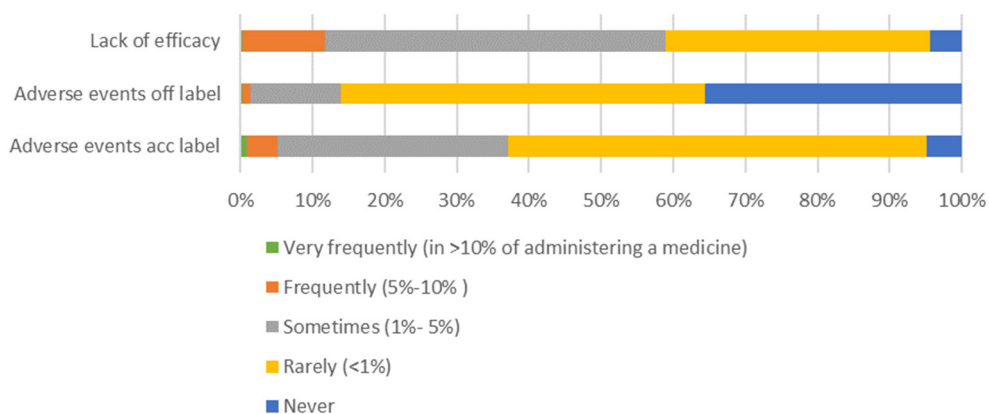
### Adverse events seen with off-label

When asked how often they saw adverse events following off-label use, 50 per cent of the respondents observed adverse events rarely (in less than 1 per cent of the off-label prescriptions), 36 per cent said they never saw adverse events following off-label use, and only 14 per cent observed them more frequently. This

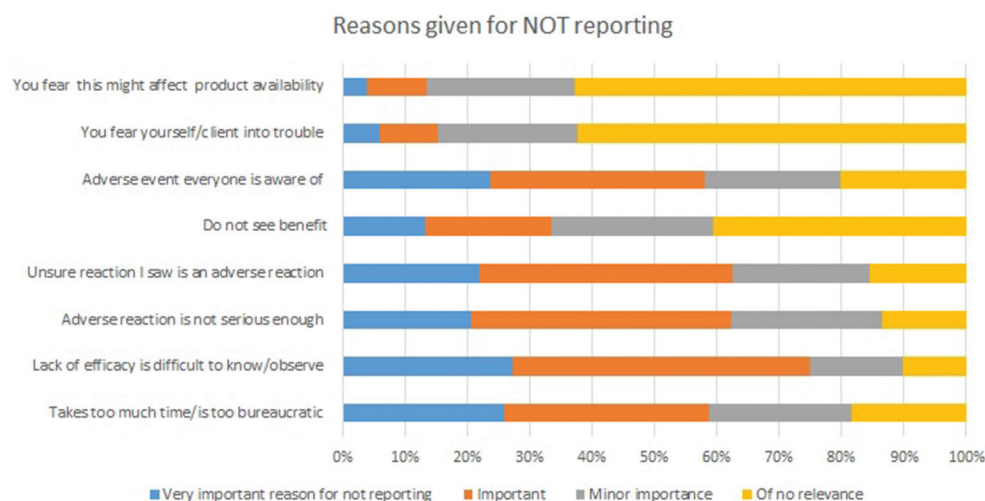
indicates that adverse events following off-label use were said to be observed less frequently (14 per cent) than with recommended use of medicines (37 per cent).

### Reasons for not reporting

The most important reason given for not reporting was that the respondents were unsure of whether the



**FIG 5:** Frequency of seeing lack of efficacy and adverse reactions off-label/on-label.



**FIG 6:** Reasons for not reporting.

event observed was really an adverse event (63 per cent (1583/2533) scored this important or very important). This was even more pronounced for lack of efficacy, where 75 per cent of the respondents scored the difficulty in knowing or observing a lack of efficacy as important or very important. Other reasons considered important or very important in discouraging individuals from reporting were that adverse events were not serious enough or were already known and that the reporting process ‘takes too much time’. Fear that reporting might impact on product availability or ‘would get the reporter or his client into trouble’ was scored as the least important reason for not reporting (Fig 6).

Other reasons given for not reporting via free text were that it is ‘not a habit’, ‘do not know how to report’, ‘forgotten’, ‘nothing was done with earlier reports’, ‘unsure if multiple medicines were given and which one caused the event’, ‘not sure if the owner administered the product correctly’ and ‘do not see the usefulness of the system’.

### Time it takes to report

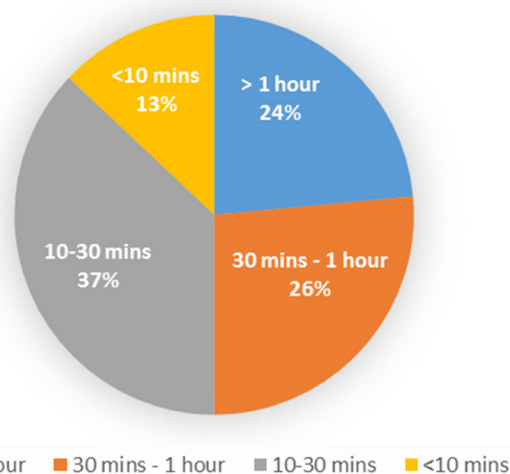
Concerning the time taken to report, half (1237/2474) reported it took more than 30 minutes, the others less than 30 minutes (Fig 7). Large differences were seen between countries. Respondents from Germany, UK and Sweden gave the lowest estimated time, while respondents from Serbia, Italy, Spain and Romania gave the longest time estimates (Fig 8). Electronic reporting was selected by 84 per cent as the preferred reporting method (respondents could select multiple options) in all countries. By phone was the second preferred method chosen by 24 per cent and paper reporting was selected by 14 per cent. Respondents were also given the opportunity to specify via free text which other methods they would prefer to use for reporting. The most frequently quoted methods were via email (14/72 times mentioned), a phone app (11/72), company

representatives (8/72) and veterinary practice software systems (5/72).

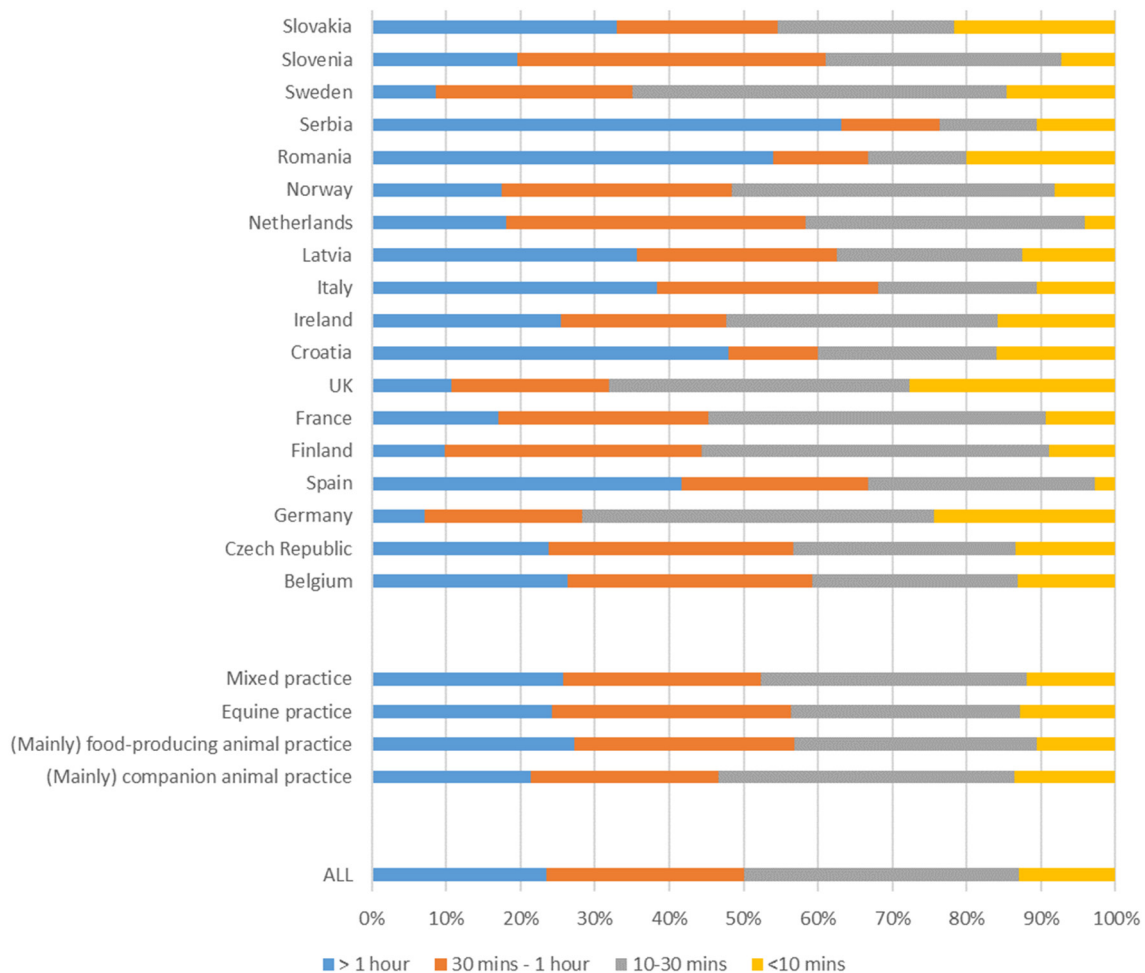
### Reporting through routes other than the competent authority

Veterinarians were asked whether they only report to the competent authority or also to alternatives such as the marketing authorisation holder. Twenty-eight per cent (779/2764) only reported to the competent authority, while 72 per cent reported to marketing authorisation holder. Extensive differences can be seen between countries, with most reporting through other routes than the competent authority in Slovakia, Belgium, The Netherlands and Italy (82 per cent, 79 per cent, 78 per cent and 77 per cent, respectively). The least reporting to others other than the competent authority was seen in Serbia and Croatia (Fig 9).

The most important reasons given for reporting to others was ‘I receive direct feedback’ (41 per cent, 827/2036), ‘it is easier’ (34 per cent), ‘I believe the person knows better and will make official report if



**FIG 7:** Time it takes to report.



**FIG 8:** Time it takes to report per country/practice type.

necessary' (17 per cent) and 'other reasons' (8 per cent). The main 'other reasons' quoted included that the pharmaceutical representative is known to them personally, making it much easier to report and to get immediate feedback. They trust the pharmaceutical representative to know their products, to know whether the adverse event they see is 'normal' or not, to maybe give advice on how to avoid it, and also said that the representative will — if necessary — report the problem himself to the authorities, which saves them time.

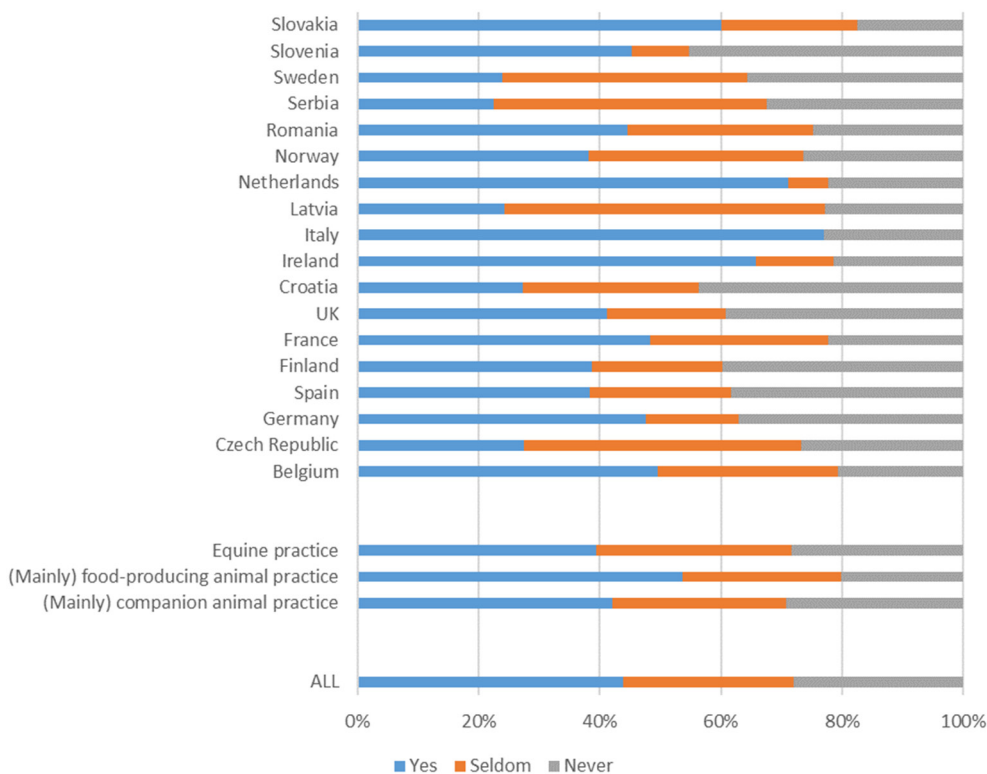
### Feedback: frequency and satisfaction

Respondents were asked whether they were satisfied with the feedback received on their reports made. Of the respondents, 53 per cent (1220/2287) replied they never received any feedback. Of those who received feedback, 25 per cent were satisfied with the feedback received and 22 per cent not really satisfied. Large differences were seen between the countries. Respondents from Italy, Norway and Spain reported most frequently to have never received feedback to their report (81 per cent, 76 per cent and 74 per cent, respectively). Respondents from France and Croatia were the most satisfied (33 per cent and 31 per cent, respectively) (Fig 10).

When asked how the reporting authority feeds back information to them about *all* reports made by veterinarians in their country, 50 per cent (1300/2588) replied they did not know, 22 per cent replied via the veterinary journal, 11 per cent via email alerts, 9 per cent via paper, 6 per cent via the website and 2 per cent via other ways. Concerning the frequency of feedback received, 46 per cent (1182/2545) never received feedback, 28 per cent received feedback one to three times a year, 17 per cent received feedback only for serious adverse events and 9 per cent more than three times yearly. Respondents from Italy, The Netherlands, Latvia and Serbia mostly replied they received no feedback at all on overall adverse event reports in their country (79 per cent, 79 per cent, 77 per cent and 76 per cent, respectively). In contrast, in Sweden, only 1 per cent of the respondents replied they never received feedback (Fig 11).

### DISCUSSION

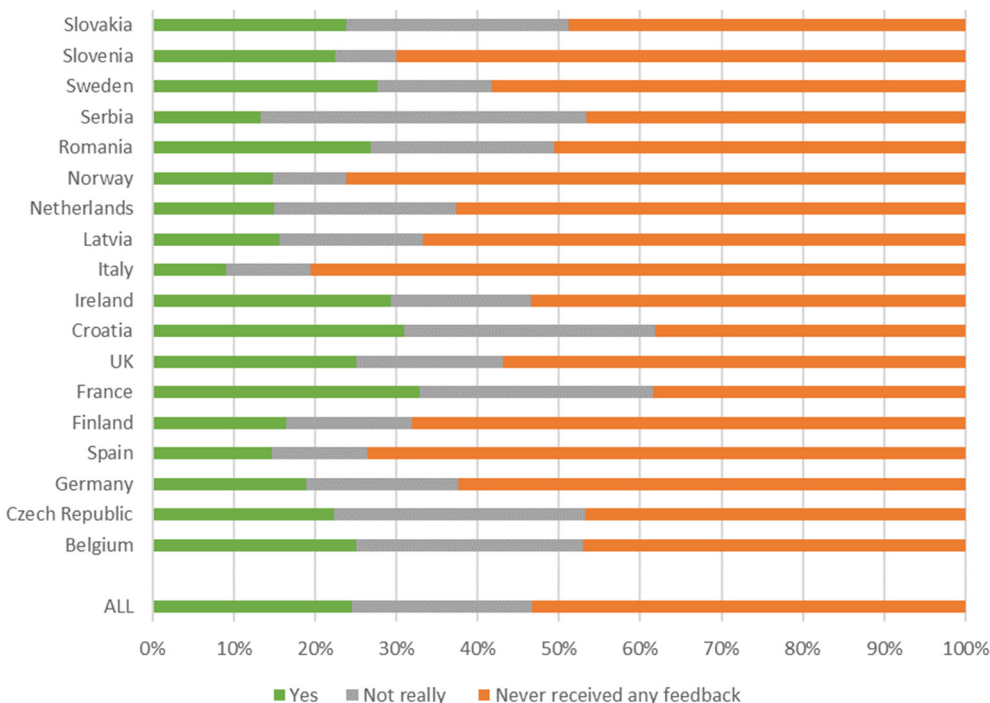
The survey was developed as an initial step for gaining an insight into reporting practices in different European countries. It is acknowledged that this was not a formally structured study based on a defined population of veterinarians. Instead the survey relied on



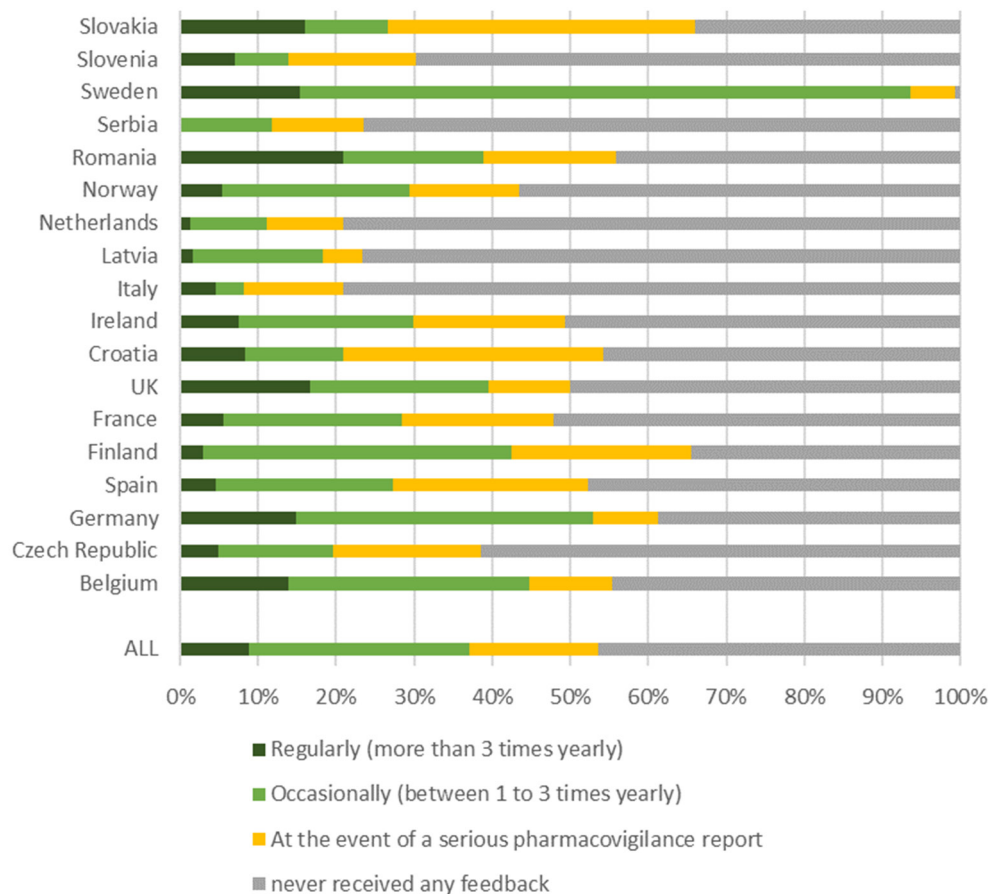
**FIG 9:** Do you report to others other than the competent authority per country/practice type.

veterinarians volunteering to answer. The survey was promoted by professional veterinary associations using a variety of methods in different countries and over a relatively short time frame. It should therefore be acknowledged that this may have biased the study and the results should be interpreted with care. However, the large number of replies (+3500 representing

3.1 per cent of the target population) with a demography of respondents similar to that of the veterinary profession in Europe (FVE 2015) suggests that the results give a good indication of the real situation. Therefore, we believe the results provide a broad insight into the main challenges and obstacles for veterinarians reporting adverse events in Europe and how



**FIG 10:** Per country: how satisfied are you with the feedback received?



**FIG 11:** Per country: feedback frequency all reports.

much information on adverse events reported flows back to them. This is an area where, to our knowledge, no previous Europe-wide published studies exist.

The pharmacovigilance system has two main goals; first, to identify adverse events in animals, human beings or the environment during or after treatment with the medicine, and second to identify lack of expected efficacy. Pharmacovigilance based on spontaneous reporting by veterinarians is a powerful tool for detecting adverse event signals of direct clinical importance and a way in which veterinarians can play a major role in the promotion of animal health, welfare and public health (O'Rourke 2016). It is however dependent on veterinary professional participation and motivation to report.

### Under-reporting: a remaining problem

The pharmacovigilance system relies mainly upon spontaneous reporting by veterinarians and in some countries by also animal owners (EMA 2016c). Some but not all Codes of Conduct oblige veterinarians to report all suspected adverse events (FVE 2000, Magalhães-Sant'Ana and others 2015, Royal College Veterinary Surgeons 2016). Non-spontaneous adverse event reports, for example, through literature, internet and social media, so far play a minor role but are a growing area of interest (EMA 2016d). The results of our survey show, however, that the majority of adverse events remain unreported. According

to our respondents, the average veterinarian sees approximately 1 adverse event in every 100 treatments given. When we use the scenario where a veterinarian prescribes or administers approximately 1000 treatments a year, this means they should see approximately 10 adverse events yearly. However, the average veterinarian makes less than one report a year. A study on under-reporting in France (Fresnay and others 2015) found that an average veterinarian would see 4.96 adverse events for companion animals per year and 2.06 for food-producing animals, which is nine times more than the average number of adverse events declared yearly by French veterinarians. This is a noteworthy finding given the extensive efforts made by the French government to promote reporting of adverse events, which led to a reporting increase of 39 per cent between 2011 and 2015 (ANSES 2016); in our survey, France was also confirmed as one of the countries where the most reports were made and where veterinarians were the most satisfied with the feedback received.

Under-reporting is not only a problem in veterinary medicine, as it is estimated that only 5–10 per cent of the adverse events seen in human medicine are reported (Edwards 2012).

### Lack of efficacy: the current pharmacovigilance system is poorly equipped

The results of our survey show that lack of efficacy is observed more frequently than adverse events (58 per cent



vs 37 per cent seeing it in more than 1 per cent of veterinary medicinal product administrations). Nevertheless, reports for lack of efficacy are seldom made, with greater than 92 per cent of the veterinarians saying they never made a report for lack of expected efficacy. The EMA public pharmacovigilance bulletin (EMA 2016c) shows that 383 out of the 14 387 adverse event reports were submitted for potential lack of efficacy concerns. Of these reports, most of them were found to be inconclusive because of insufficient data or lack of detailed information. The French report (ANSES 2016) of 2014 estimated 10 per cent of reports being for lack of efficacy, but also found that often definitive conclusions cannot be drawn on whether it is genuine lack of expected efficacy of the product.

There are ongoing discussions on the use of the pharmacovigilance system to obtain information and feedback on therapeutic failures, so as to identify potential resistance issues (EU guidelines 2015). Given how difficult it is to demonstrate lack of expected efficacy, knowing resistance testing is easy and that Member States routinely carry out surveys on resistance, the pharmacovigilance system does not seem to be appropriate for this. Moreover, the current pharmacovigilance system seems poorly equipped to demonstrate lack of efficacy.

### Pharmacovigilance and off-label use: a difficult relationship

Veterinarians regularly have to resort to off-label use under the prescribing cascade (EU Directive 2001/82), namely the use of a medicine outside the conditions of the marketing authorisation. In addition to allowing treatment for a condition or species for which no authorised medicines exist, off-label use allows veterinarians to adopt new practices based on emerging evidence, to treat animals individually, choosing the product and duration of treatment based on infectious agent, animal and pharmacology, and can accommodate innovation in clinical practice (Stafford 2008). While it could be expected that more adverse events would be seen with off-label use, the veterinarians answering our survey reported seeing less adverse events with off-label use. The French Agency (ANSES 2016) found that around 30 per cent of the reports made in 2014 and 2015 were for products used off-label. Off-label use however gives rise to uncertainties in the pharmacovigilance system (White Hall Training 2016), in such a way that in the human pharmacovigilance field a specific reflection paper was drafted (EMA 2016a) and Questions and Answers were developed to address these. Overall, it is important to extend the reporting of adverse events with products used off-label and to use these adverse events in the same way as those relating to authorised indications. This information can be used to closely monitor the way products are being used in practice. Off-label use clearly plays a potentially important role in contributing to the overall safety profile of medicinal products and could play a role in extending product marketing authorisations to more species or more indications.

### Reporting through routes other than the competent authority

Most veterinarians responded that at times they report through routes other than the competent authority, mostly to the marketing authorisation holder, that is, the pharmaceutical company responsible for the product. Some preferred this route of reporting as they found it easier and quicker, and they personally knew the individual they were reporting to. Marketing authorisation holders have the obligation to communicate all serious adverse events reported to them to the competent authority within 15 days and all serious and non-serious at set intervals in the form of periodic safety update reports. In some countries, reports reach the competent authority also through the poison centres; for example, in Belgium 32 per cent of the reports in 2014 came from the Belgian Poison Centre on the basis of calls of animal owners, veterinarians or physicians (BCFI/CBIP vet 2016).

### Why veterinarians are not reporting

The main reasons given by veterinarians for not reporting were that they were unsure that what they observed was truly an adverse event or that the event was not serious enough. It also took too much time to report, time which is not reimbursed. Half of respondents estimated it took more than 30 minutes to gather all required data, complete and submit a report. The form to fill in and data to submit are different between countries, which can explain the time difference. With respect to not reporting lack of expected efficacy, the most important reason given was that they were unsure they actually observed lack of efficacy. As the availability of rapid diagnostics is still very limited and, if available, often cost more than the treatment, in most cases veterinarians have to rely on empirical treatment. So when lack of efficacy is observed, it is difficult to differentiate between a real lack of efficacy and possibly the incorrect diagnosis. This is especially valid in poly-medication treatment. In human medicine, the obstacles seen are similar, relating to the actual diagnosis of the adverse event, problems relating to lack of time, problems relating to the organisation and activities of the pharmacovigilance system, and problems relating to potential conflicts (Vallano and others 2005).

In human medicine, it is reported that under-reporting is caused by complacency (the belief that very serious adverse events are well documented by the time a medicine is marketed), insecurity (the belief that it is nearly impossible to determine whether a medicine is responsible for a particular adverse event), diffidence (the belief that reporting should only be done if there is certainty that it is related to the use of a particular medicine), indifference (the belief that a single case that an individual physician might observe could not contribute to medical knowledge), ignorance (the belief that it is only necessary to report serious or unexpected adverse events) and fear of medico-legal consequences (Palleria and others 2013).

It should also be recognised that in some countries only veterinarians and marketing authorisation holders

can report, while in other countries animal owners or other persons involved can also make a report. Generally, most reports come from veterinarians and marketing authorisation holders; for example, greater than 90 per cent of the French reports (ANSES 2016) and more than 99 per cent in Ireland (HPRA 2015).

### The feedback system needs improving

With 75 per cent of the veterinarians unhappy about the feedback received and more than half saying they never received feedback at all, it is not surprising that reporting rates remain low. It is clear that the feedback system needs urgent improvement. It was also recognised that several countries publish comprehensive public pharmacovigilance reports at regular intervals such as in France (ANSES 2016), the UK (VMD 2016) and Ireland (HPRA 2015). Despite these publications, many veterinarians still answered that they never received feedback. This means they are either not aware of these reports or they do not recognise these reports as feedback on their individual reports made. Searching on the websites of the different competent authorities, the authors found that these reports are often very difficult to locate, and in most cases it was not possible to search for reports on a specific active substance. Similar feedback issues exist in the human pharmacovigilance (Edwards 2012), and the issue was also recognised by EMA reflection paper on promoting pharmacovigilance (EMA 2015b).

### How to improve reporting

The best way to motivate reporters is to demonstrate that the reports they submit are indeed useful and enable the use of veterinary medicinal products to be improved (ANSES 2016). Therefore, in order to increase spontaneous reporting, there is a need to make reporting easier (eg, by developing mobile apps, to allow reporting via social media, etc), to improve veterinarian awareness of the importance and the value to them of reporting, and to greatly improve the feedback. Another way to simplify reporting could be through the practice management system software; however, it must be recognised that a great number of completely different systems exist, which poses practical challenges. In addition, it could be possible to follow a practice used in human medicine, where priorities for spontaneous reporting are defined in order to select types of more useful reports. However, it is unknown if this would be workable in the veterinary setting (Vallano and others 2005).

It would be also beneficial for European and NCAs for pharmacovigilance to improve structural relationships with veterinary organisations. This already exists successfully in some countries.

In addition to spontaneous reporting, the collection of non-spontaneous adverse events reports should be promoted. For new products coming onto the market or for products with potential safety concerns, marketing authorisation holders should be encouraged to proactively

search non-spontaneous sources of information on the efficacy and safety of their products.

Pharmacovigilance based on spontaneously reported data from veterinarians is a powerful tool for detecting adverse events of direct clinical impact. However, it is dependent on veterinary professional participation, and our survey confirms massive under-reporting. It also shows that the system is poorly equipped to deal with lack of expected efficacy, with only few cases reported and most found to be inconclusive because of insufficient data or lack of detailed information. In order to improve adverse event reporting, there is a need to make reporting easier (eg, by developing mobile apps, facilitating reporting via practice management system software, enabling reporting via email, etc) and to increase awareness of the importance and the value of reporting for veterinarians. Feedback in many countries is lacking and the feedback system should be greatly improved. The best way to motivate reporters is to demonstrate the importance and value of the reports they submit and how reporting enables the use of medicinal products to be improved. It would be beneficial for European and NCAs for pharmacovigilance to develop structural relationships with veterinarian organisations. For new products coming on the market or products with concerns, the marketing authorisation holder should be encouraged to do proactive searching for non-spontaneous data on the effectivity and safety of their products. The major role veterinarians can play in improving animal health, welfare and public health through reporting adverse events needs to be further promoted.

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**Data sharing statement** Full data sets available upon request to the corresponding author.

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