Assessment of Paratuberculosis international official reporting in Europe using the information supplied to the WOAH by the National Veterinary Services (NVS)

Angela Fanelli*, Michela Galgano, Alessio Sposato and Domenico Buonavoglia

Department of Veterinary Medicine, University of Bari "Aldo Moro", Str. Prov. per Casamassima Km 3, 70010 Valenzano (BA), Italy

**Corresponding author at: Department of Veterinary Medicine, University of Bari "Aldo Moro", Str. Prov. per Casamassima Km 3, 70010 Valenzano (BA), Italy. E-mail: angela.fanelli@uniba.it.*

Veterinaria Italiana 2022, **58** (2), 215-224. doi: 10.12834/VetIt.2625.16709.3
Accepted: 22.12.2021 | Available on line: 31.12.2022

Keywords
Paratuberculosis, *Mycobacterium avium* subsp. *paratuberculosis*, Epidemiology, Survival analysis, Cox proportional hazards regression analysis.

Summary
The present study characterizes the epidemiological situation of Paratuberculosis (PTB) in Europe during the last 24 years, using the information officially reported to the World Organisation for Animal Health (WOAH) by the National Veterinary Services (NVS) of the European countries. The prevalence of PTB at country level was described during the study period. A Cox proportional hazards (PH) regression analysis was implemented to evaluate the reporting behaviour. The most affected countries were found in southern and western Europe, whereas PTB presence was lower in northern and eastern Europe. PTB was routinely declared as a notifiable disease in 65% of the countries. Less than 50% of the countries routinely implemented passive surveillance, and only 19%, reported active surveillance for disease detection. Results of the Cox PH regression indicate that the Gross National Income (GNI) per capita and the application of active surveillance significantly influence the recurrence of PTB reporting. In countries with lower and upper middle income, the hazard of recurrence is 0.13 and 0.18 times lower than in countries with high income. The hazard of recurrence in countries that infrequently and moderately applied active surveillance is 1.99 and 1.65 times higher than in countries that routinely applied active surveillance. Findings of this work highlight an important variation in the reporting behaviour, disease status and surveillance across Europe.

Introduction

Paratuberculosis (PTB), also known as Johne's Disease, is a contagious and chronic gastrointestinal infection caused by *Mycobacterium avium* subsp. *paratuberculosis* (MAP), affecting mainly domestic and wild ruminants. In many European countries, the herd-level prevalence is estimated to be higher than 50% (Nielsen and Toft 2009). PTB is usually subclinical, and MAP can persist undetected for many years within a herd. Clinical signs are primary observed in the late phases of infection. These include weight loss and unresponsive watery diarrhoea. PTB causes substantial economic losses to the cattle industry due to decreased milk production and reproductive performance, reduction of the slaughter value and increased premature culling, which in turn increases the replacement costs. Moreover, animals infected with MAP have higher susceptibility to other disease, thus the quantification of the real economic impact is challenging (Garcia and Shalloo 2015). The overall financial impact in the EU is roughly € 300 M/year (EFSA Panel on Animal Health and Welfare 2017). The estimates of the total annual economic losses per cow in infected areas are: a) in dairy herds € 234 in France (Dufour *et al.* 2004), GBP 27 in UK (Stott *et al.* 2005), up to € 67 in the Netherlands (Groenendaal *et al.* 2002), b) in suckler herds € 40 in French herds (Dufour *et al.* 2004), GBP 16 in British herds (Humphry *et al.* 2001), from € 10 (small herds) to € 28 (large herds) in the Netherlands (Groenendaal *et al.* 2002).

The risk of infection in cattle decreases after six months of age. Many animals are infected during the first weeks of life through the fecal-oral route or through the consumption of milk and colostrum. The susceptibility to the infection is related to the maturation of cellular immunity and the difficulties of young animals to cope with intracellular pathogens as MAP. However, the clinical symptoms of PTB are usually seen in adults, as a consequence of the long incubation period (1.5-2 years) (Koets *et al.* 2015, Manning and Collins 2001).

There are strong associations between MAP and the Crohn's disease in humans, but the zoonotic potential of the agent is still poorly understood (McNees *et al.* 2015). The public health concern, combined with the economic losses in the livestock industry, has driven to the implementation of control programmes. In addition, as MAP DNA was found both in commercial cow's milk and infant powder (Hruska *et al.* 2011), agreements were signed between countries to ensure the exportation of certified PTB-free dairy products (Gamberale *et al.* 2019). For instance, Italy developed guidelines to meet the request of China, India and Russia, that are the leading importers of Italian milk and dairy-products (Luini *et al.* 2013).

The management of PTB presents several challenges regarding diagnosis, treatment, and prevention. A potential constrain in the control of mycobacterial diseases is the existence of wildlife reservoirs, being numerous species susceptible to MAP. In particular, deer and wild rabbits could play a role in MAP infection of cattle or sheep through contaminated pastures (Carta *et al.* 2013).

A wide range of diagnostic tests exists, including bacterial culture, polymerase chain reaction (PCR) on faecal samples, and enzyme-linked immunosorbent assay (ELISA) for serum or milk. However, none of the available tests is recommended to be used alone by the WOAH Manual of Diagnostic Tests and Vaccines for Terrestrial Animals, which assesses standard methods for disease diagnosis (OIE 2021b). Serological tests have also a low sensitivity if they are applied in the earlier stage of disease or in case of subclinical infection, resulting in false-negative results. Moreover, false-positive results can be due to cross-reactivity with other *Mycobacterium* species (e.g. common antigens shared between MAP and *Mycobacterium bovis*) (Garcia and Shalloo 2015).

On a European scale, the surveillance of PTB is heterogeneous. In fact, some countries apply a strict mandatory control programme [e.g., Sweden implements stamping out policy (SFS 1999:657)[1]], while others have voluntary regional programmes or no control programmes at all. Preventive and control measures include vaccination, testing, and herd management based on a producer's resources, facilities, and operation. Unfortunately, the implementation of PTB vaccination has been limited as a result of the cross-reactions with tuberculosis diagnostic tests in vaccinated animals (Garcia and Shalloo 2015).

Because of the regional heterogeneous framework, only a questionnaire survey inquiring about the activities of the national reference institutes, dairy and farmers' organizations could provide useful insights into the actual PTB epidemiological situation. In this regard, a recent review based on questionnaires sent to PTB experts pointed out that the reduction of the disease prevalence is the main objective of PTB control programmes in many countries (Whittington *et al.* 2019). Additionally, it showed that animal health is the main reason to adopt a control programme, followed by the objective of reducing the economic losses associated with the disease. Conversely, public health is a main driver only for few countries (Whittington *et al.* 2019).

PTB is a WOAH listed disease, with the obligation for the Member States to report the disease. Nevertheless, the WOAH does not provide guidance on how to control PTB, and there is no case definition available in the WOAH Terrestrial Animal Health Code. Given the lack of international reporting standards, the absence of a disease freedom definition, and the difficulties in disease detection, it is not surprising that PTB is largely underreported worldwide (Whittington *et al.* 2019).

Considering that official PTB data at the European level may be particularly useful to improve the disease surveillance programmes and management and very helpful in health policy planning, the objective of this study was to analyse the PTB notification and reporting behaviour of the European countries.

Materials and methods

Data used to assess the PTB status of the European countries[2] derived from two WOAH databases: Handistatus II for the period 1996-2004 (OIE 2020a) and WAHIS for the period 2005-2019 (OIE 2020b). The information contained in these systems is submitted to the WOAH by the National Veterinary Services (NVS) of Member Countries every six months.

Per each country, the yearly disease status was calculated over the last 24 years as follows: a) "disease present" whether the country declared the presence of PTB at least in one semester, b) "disease absent" whether the country declared the absence of PTB in both semesters and in case of an absence in one semester plus a missing record in the other semester, c) not available (NA) if missing records were present in both semesters.

[1] Swedish Ministry of Agriculture.2018. Epizootic Act (SFS1999:657). http://rkrattsbaser.gov.se/sfst?bet=1999:657.

[2] Member countries of the WOAH Regional Commission for Europe: https://www.woah.org/fileadmin/Home/eng/About_us/docs/pdf/CR2018/2020_Commission_Europe_A.pdf.

Distribution of PTB in Europe from 1996 to 2019

To describe the prevalence of PTB at country level we computed the number of years for which the disease was reported as present over the number of years for which information was provided by each country. A bar plot was created for graphical representation.

Survival analysis

A Cox proportional hazards (PH) model was used to assess the PTB notification behaviour of the European countries and evaluates the general level of countries reporting. The PH model is an appealing analytic method to compute the hazard ratio, which provides an estimate of relative risk of events (outcome of interest) to epidemiologists (Kleinbaum 1996).

Description of the outcome variable (survival event)

For the purpose of this study, an event is considered as the reporting of PTB as present at country level in domestic ruminants (1 if the disease was reported present or 0 if the disease was reported absent).

Description of the explanatory variables

Twelve explanatory variables retrieved from different public databases were used in this study. The variables were chosen based on their potential influence on disease reporting and notification (Table I). A descriptive analysis of the ones directly related to disease detection capabilities according to the chapter 1 of the WOAH Terrestrial Animal Health Code (veterinary workforce, disease notification and surveillance - OIE 2021a) is provided in the results section.

Some of the variables were standardized as explained below.

The median number of veterinarians (both private and public professionals) involved in animal health activities over the 24 years was normalized by the livestock unit (LSU) as defined by the European Commission[3]. The information on the veterinary workforce was retrieved from the WAHIS interface whereas the data on livestock from the Food and Agriculture Organization of the United Nations (FAOSTAT 2020). The quantitative variable was then transformed into a categorical variable using

[3] https://ec.europa.eu/eurostat/statistics-explained/index.php/Glossary:Livestock_unit_(LSU).

Table I. *Explanatory variables retrieved from different sources to build the Cox proportional-hazards model for the occurrence of Paratuberculosis (PTB) in the European countries.*

Variable	Description	Source
Active Surveillance*	Reporting the implementation of active surveillance to the WOAH	WAHIS INTERFACE https://wahis.woah.org/#/home
Passive Surveillance	Reporting the implementation of passive surveillance to the WOAH	WAHIS INTERFACE https://wahis.woah.org/#/home
Disease notification	Reporting the disease notification to the WOAH	WAHIS INTERFACE https://wahis.woah.org/#/home
Laboratory capacity for PTB diagnosis (presence\ absence)*	Reporting the laboratory capacity for PTB diagnosis to the WOAH	WAHIS INTERFACE https://wahis.woah.org/#/home
PTB status in wildlife	Reporting the presence of PTB in wildlife to the WOAH	WAHIS INTERFACE https://wahis.woah.org/#/home
Veterinary Workforce*	The median number of veterinarians involved in animal health activities over the 24 years was normalized by livestock unit (LSU)	WAHIS INTERFACE https://wahis.woah.org/#/home
Cattle and buffaloes per agricultural land*	FAOSTAT agri-environmental indicator on livestock patterns	FAOSTAT http://www.fao.org/faostat/en/#home
Sheep and goat per agricultural land*	FAOSTAT agri-environmental indicator on livestock patterns	FAOSTAT http://www.fao.org/faostat/en/#home
Press of freedom index*	The degree of freedom available to journalists (as a proxy for country transparency in disease reporting)	WORLD PRESS FREEDOM INDEX https://rsf.org/en/ranking
Geographic Regions	Sub-regions based on UN classification	Statistics Division of the United Nations Secretariat https://unstats.un.org/unsd/methodology/m49/
EU/ NON-EU countryv	Countries belonging or not to the European Union	EUROPEAN UNION https://europa.eu/european-union/about-eu/countries_en
Income level*	Income classification based on Gross National Income (GNI) per capita (current US$)	THE WORLD BANK https://data.worldbank.org/indicator/NY.GNP.PCAP.CD

*Variables included in the process of model building after checking for collinearity.

the quartiles to obtain 4 classes of veterinary workforce LSU:

a. “Low” (first quartile)
b. “Low-Medium” (second quartile)
c. “High” (third quartile)
d. “Very High” (fourth quartile)

The percentage of years of positive reporting over the number of years for which the country reported data was computed for the remaining factors included in the analysis: 1) the application of active and passive surveillance, 2) the obligation of disease notification at country level, and 3) the PTB status in wildlife. Afterwards, the percentage values were converted into categories as specified below.

Surveillance (passive and active):

a. “Never Applied” if the country never applied surveillance,
b. “Infrequently applied” if the country applied surveillance up to 25% of the study period,
c. “Moderately applied” if the country applied surveillance from 26 to 50% of the study period,
d. “Frequently applied” if the country applied surveillance from 51 to 75% of the study period,
e. “Routinely applied” if the country applied surveillance from 76 to 100% of the study period.

Disease notification:

a. “Never declared” if the country never declared PTB as a notifiable disease,
b. “Infrequently declared” if the country declared PTB as a notifiable disease during up to 25% of the study period,
c. “Moderately declared” if the country declared PTB as a notifiable disease from 26 to 50% of the study period,
d. “Frequently declared” if the country declared PTB as a notifiable disease from 51 to 75% of the study period,
e. “Routinely declared” if the country declared PTB as a notifiable disease from 76 to 100% of the study period.

PTB wildlife status:

a. “Never reported” if the country never reported the status of PTB in wild animals,
b. “Reported absence” if the country reported the disease as absent over the whole study period,
c. “Low reporting” if the country reported the disease as present up to 33% of the study period,
d. “Medium reporting” if the country reported the disease as present from 34 to 66% of the study period,
e. “High reporting” if the country reported the disease as present from 67 to 100% of the study period.

QGIS 3.2 (QGIS Development Team 2017) was used to map and show the spatial patterns of the most relevant variables.

Statistical analysis

The PH model was used to identify the factors associated with the reporting of PTB recurrence in Europe. The term “recurrence” is used as in the WOAH Terrestrial Animal Health Code to intend the detection of the disease by the veterinary services following a report that declared the outbreak(s) ended (OIE 2021a)

This is a semiparametric technique that is commonly used for survival analysis of recurrent events. Given the correlated nature of the data, the generalized estimating equations (GEE) approach was implemented. Before building the model, we checked for collinearity in the associations between predictors using chi-square analysis and the Pearson's correlation coefficient for categorical and continuous variables, respectively. Only the most significant variables within each set of collinear factors were used.

The “survival” package in R software (R Core Team 2018) was used to build the model (Therneau 2020). Backward stepwise variable selection was performed to retain the model with the smallest Akaike Information Criterion (AIC) among all competing models (Akaike 1973). Eventually, the good-ness of fit (GOF) of the final model was evaluated with the Wald test, and the PH assumption were assessed both graphically, checking the Schoenfeld residuals (Schoenfeld 1982), and by the GOF tests proposed by Harrell (Harrell 1986).

Results

Only 43 countries from the European region were considered in the study, selecting the ones that regularly provided data to the WOAH. Figure 1 shows the percentage of years for which PTB was reported as present for each country. Southern and western Europe appeared to be the most affected, whereas the presence of PTB is lower in northern and eastern Europe.

The Veterinary workforce was heterogeneously distributed, with 28% (CI95% 15-41%) of the countries characterized by “Low workforce” of veterinarians, 26% (CI95% 13-39%) “Low-Medium workforce", 19% (CI95% 7-30%) "High workforce", and 28% (CI95% 15-41%) "Very High workforce" (Figure 2). In general, the highest values for veterinary workforce were found in the eastern part of the study area, while the lower values in northern and central Europe.

Figures 3 shows that PTB was a notifiable disease in most of the European countries. In fact, 65% (CI95%51-79%) of the countries reported the disease as notifiable during more than 75% of the study period ("Routinely declared") and only 12% (CI95%2-21%) never declared the disease as notifiable. These include Armenia, Denmark, France, Georgia, and Hungary. With regards to the remaining countries, 9% (CI95% 0.6-18%) were classified as "Frequently declared", 5% (CI95% -2-11%) as "Moderately declared", and 9% (CI95% 0.6-18%) as "Infrequently declared".

Figure 4 and Figure 5 show the application of passive and active surveillance during the study period. Less than 50% (37%, CI95% 23-52%) of the countries "Routinely applied" the passive surveillance, 12% (CI95% 20-21%) of countries were classified as "Frequently applied", 12% (CI95% 20-21%) as "Moderately applied", 2% (CI95% 0.6-18%) as "Infrequently applied", and 37% (CI95% 23-52%) as "Never applied".

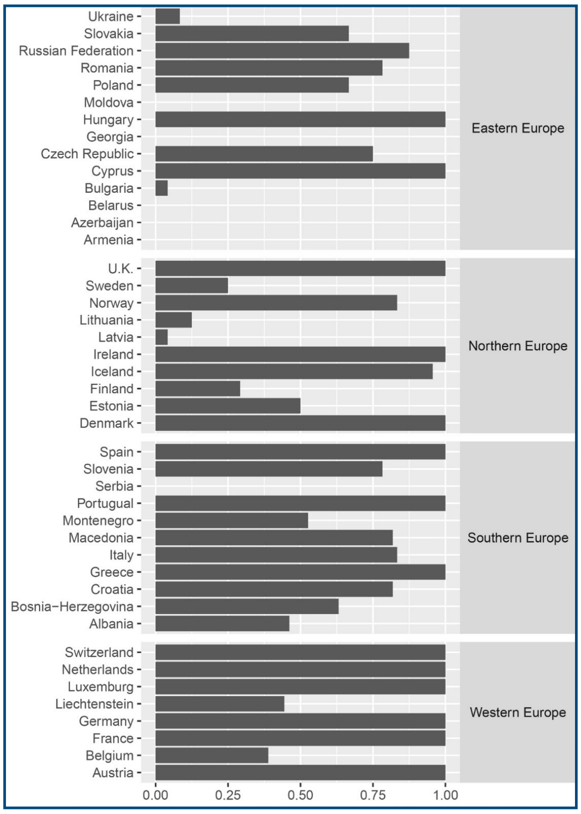

Figure 1. *Paratuberculosis (PTB) occurrence in 46 European countries: prevalence during the study period (1996-2019).*

The majority (42%, CI95% 27-57%) of the countries reported having "Never applied" active surveillance. Hence, only 8 (19%, CI95% 7-30%) countries routinely applied this measure, whereas the remaining countries as follows: 16% (CI95% 5-27%) "Frequently applied", 16% (CI95% 5-27%) "Moderately applied", and 7% (CI95% -0.6-15%) "Infrequently applied".

Results of the PH model indicated the following factors as significantly associated with the PTB recurrence: the Gross National Income (GNI) per capita (current US$) and the application of active surveillance during the study period (Table II).

In countries with lower middle income and upper middle income, the hazard of recurrence was 0.13% (CI95% 0.04-0.5%) and 0.18% (CI95% 0.08-0.4%) times the hazard (87% and 82% decreased) when compared with countries with high income. The hazard of recurrence in countries that "Infrequently" and "Moderately" applied active surveillance was 1.99% (CI95% 1.1-4.05%) and 1.65% (CI95% 1.05-2.58%) times higher than in countries that "Routinely applied" the control measure during the study period. Nevertheless, the categories "Never

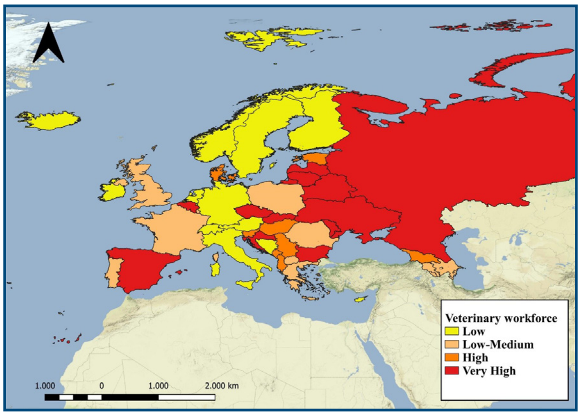

Figure 2. *Spatial distribution of veterinary workforce in Europe (1996-2019).*

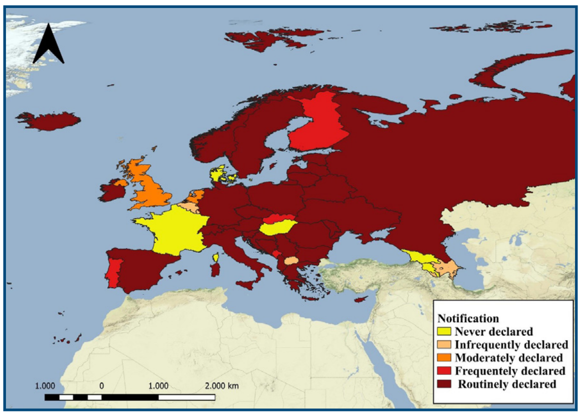

Figure 3. *European countries reporting Paratuberculosis (PTB) as a notifiable disease during the study period (1996-2019).*

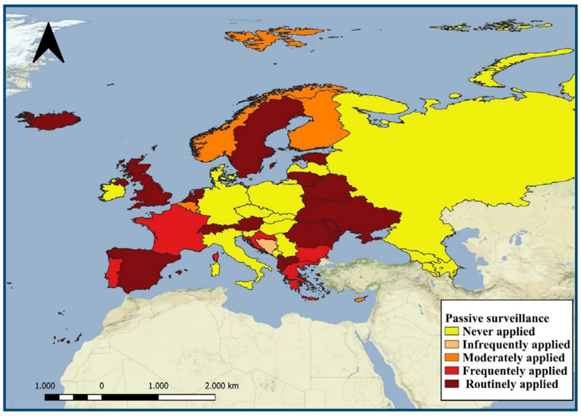

Figure 4. *European countries reporting the application of passive surveillance for Paratuberculosis during the study period (1996-2019).*

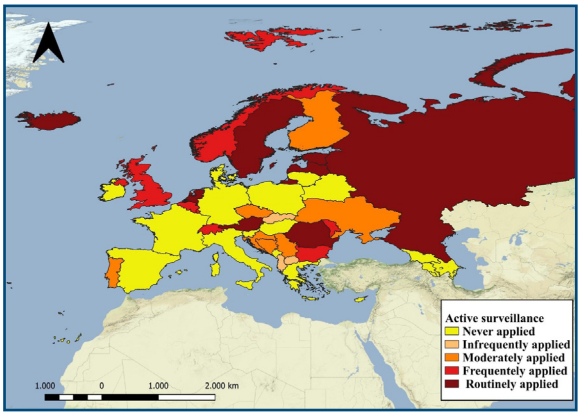

Figure 5. *European countries reporting the application of active surveillance for Paratuberculosis during the study period (1996-2019).*

applied" and "Frequently applied" did not significantly differ compared with "Routinely applied".

With regards to the remaining variables, the laboratory capacity for PTB diagnosis was not a significant factor (p-value = 0.12), while the hazard ratio of the press of freedom (as a proxy for the transparency in disease reporting) was very close to 1, indicating that this factor does not have an influence on the disease reporting.

Discussion

This study assesses the epidemiological features of PTB at European level, using the official information reported by the NVS to the WOAH. Only few studies provided a wide overview of the international reporting of diseases at regional scale so far (e.g. Fanelli *et al.* 2020, Meske *et al.* 2021), being mostly focused on national or subnational level. Thus, the objective of this work was to assess the reporting of PTB at European level, as well as the disease dynamics during the last 24 years. This study also provides important information about countries preparedness and reactivity in disease control, including the veterinary workforce and the implementation of relevant preventive and control measures. This information is very useful for any risk assessment of disease introduction and spread at national and regional level (Zepeda *et al.* 2001, Fanelli and Buonavoglia 2021).

Table II. *Cox proportional-hazard (PH) regression analysis of Paratuberculosis (PTB) recurrence in Europe.*

Variable	Hazard Ratio	95% CI lower	95% CI upper	p-value
GNI				
High income	-	-	-	-
Lower middle income	0.13	0.04	0.5	0.003
Upper middle income	0.18	0.08	0.4	< 0.001
Press of freedom index	1.02	1.01	1.03	0.003
Laboratory capacity for PTB diagnosis	1.37	0.92	2.05	0.12
Active surveillance				
Routinely applied	-	-	-	-
Frequently applied	1.42	0.82	2.45	0.2
Moderately applied	1.65	1.05	2.58	0.03
Infrequently applied	1.99	1.1	4.05	0.05
Never applied	0.86	0.58	1.26	0.4

Wald test = 33.71 on 8 df; p-value=5e-05.

One of the strengths of the data used is represented by the standardized system adopted by the WOAH for data collection. These data reflect the level of the countries reporting as well as the efforts, the transparency and efficiency of the NVS. The WOAH carefully verifies the information reported by the NVS as soon as it is received. Furthermore, to ensure the transparency in the reporting of animal diseases, the WOAH performs an active search activity for non-official information and rumors. Considering the above, the information stored in WAHIS can be considered as the most reliable picture of the international situation of notifiable animal diseases, even if discrepancies with the real situation "on the field" are always possible. The absence of PTB notification in some semesters may not reflect the true absence of the disease. In fact, the information reported by the Member States depends not only on the disease status, but also on the level of reporting and the surveillance programmes in place.

In accordance with the WOAH reporting system, international disease notification relies on the country national surveillance system (Cáceres *et al.* 2017). In this sense, data on disease presence have 100% specificity, whereas the reliability of the information on disease absence (true absence) depends on several factors related to countries preparedness, resources, and transparency. Based on the results of this study, the epidemiological information currently available on PTB is still limited, with a large percentage of countries not notifying the disease. The problem of a false absence (lack of sensitivity) in surveillance and monitoring systems is a well-known problem, that affects the capacity of obtaining an accurate and precise understanding on the real distribution of diseases. This issue affects mainly diseases that are either difficult to diagnose or diseases that are neglected (Fanelli *et al.* 2020). A similar situation might be observed in wildlife disease when there is no surveillance system in place (Fanelli *et al.* 2020, Gontero *et al.* 2020, Tizzani *et al.* 2020, Fanelli 2021). In fact, although several countries have made significant progress in the transparency of diseases reporting to the WOAH, there is some room for improvement (Cárdenas *et al.* 2019). During our analysis, we found some discrepancies between the official data reported by the NVS and the information available in the scientific literature. For instance, Serbia never reported the PTB as present during the last 24 years (Figure 1), but antibodies against MAP were detected in sheep with ELISA test by Vidić (Vidić 2014). Discrepancies with official information were also found for Bulgaria, whose veterinary services reported officially PTB present only once, although the disease is considered endemic in both wild and domestic ruminants (Savova *et al.* 2016). These discrepancies might be due to a lack of communication between the NVS and Research Institutes as well as to a clear PTB case definition in the WOAH Terrestrial Animal Health Code. Indeed, clearly defined criteria (laboratory, epidemiological and clinical) for a comprehensive case definition of PTB could improve the reporting, informing the countries under which circumstances PTB must be notified.

Broadly speaking, PTB is likely to be present in every country of the European Region, excepting Sweden where the prevalence is low and all recent cases have been linked to imported animals (Whittington *et al.* 2019). An unusual/inconsistent reporting has been detected also for Russian Federation since it reported not implementing passive surveillance while declaring the implementation of active surveillance throughout the study period. This does not happen often as the implementation of active surveillance tends to be coupled with passive surveillance activities.

All these findings highlight: i) the need of clarifying PTB case definition, ii) a lack of connection between the NVS and Research Institutes that does not facilitate a proper flow of information, iii) a lack of transparency, resources and/or efficiency of surveillance systems. It is important to consider that the causes of underreporting may vary from country to country.

Although the notification of PTB is mandatory in most of the countries, only few of them apply proper surveillance for disease monitoring. Moreover, there are inconsistencies between the control measures applied by some countries and the one reported to the WOAH. A case in point is represented by Italy which, despite the existence of national guidelines including both a passive surveillance system (clinical case reporting) and a voluntary active surveillance system (Whittington *et al.* 2019), never reported the application of PTB control measures to the WOAH throughout the study period. This work shows that only few countries apply “frequently” or “routinely” passive surveillance, and even a lower number applies active surveillance. According to the official information, less than 50% of the countries implement passive surveillance, and only Northern European countries declare to apply active surveillance over the last 24 years. In eastern Europe, the framework is heterogeneous: some countries, as Poland, “Never reported” active surveillance while others, like Moldova “Frequently reported”, and Romania “Routinely reported” the application of this control measure. There are several reasons for not implementing a PTB surveillance and control programme. Probably, one of the most relevant is that animal health resources are usually deployed to tackle other priority diseases (Nielsen 2009). In addition, as shown in figure 2, there is also a potential shortage of veterinary personnel with respect to the animal population of the countries. Because of the potential human resources constrain, countries may tend to focus their efforts on more impacting diseases. It is also important to consider that PTB is not in the category A and B of the EU Animal Health Law 429/2016, but in category E (diseases for which surveillance is needed) (Whittington *et al.* 2019).

The PH model indicates that the risk of PTB recurrence is higher in high-income countries, which are supposed to be the countries with better animal health conditions. This finding needs to be interpreted carefully as it may reflect a higher quality of PTB monitoring (better sensitivity of national surveillance systems) rather than an actual worse epidemiological situation of the disease.

Among the countries reporting a monitoring system in place for the disease, those that “Infrequently” and “Moderately” applied active surveillance, resulted to have a risk of PTB recurrence two times higher than countries which “Frequently” used this measure. It should be noted that active surveillance activities tend to be expensive, and time-consuming, therefore only the richest countries in Europe might afford active surveillance targeting PTB. Generally, the objectives of PTB active surveillance are: i) the infection control at regional/national level, ii) market assurance of animal products (where infection is endemic); ii) demonstration of herds freedom (where it is believed the infection is not present). Norway and Sweden, which rarely report PTB, not only implement active surveillance, but they also have developed performance indicators for their control programmes: the increase in the participation rate of herds, meeting targets in the number of low risk, free or certified herds and reductions in the number of infected animals or clinical cases detected (Whittington *et al.* 2019). Considering the above, PTB appears to be more present in high-income countries due to a better surveillance activity that reduces the possibility of false absence. Nevertheless, among the high-income countries, the ones that routinely applied active surveillance programmes are managing to reduce the risk of disease recurrence.

One of the major strengths of a surveillance system is the veterinary workforce, which is quite heterogeneous in Europe as shown in Figure 2. Although this variable was not retained in the PH model, it is well known that limited veterinary workforce in animal public health field represents a constraint for successful disease control. A recent study demonstrated a strong relationship between the number of veterinarians and PTB status of countries. The authors found that the disease was enzootic in countries with a low number of veterinarians engaged in animal health activities (Fanelli, Buonavoglia, *et al.* 2020). It should be considered that the success of a surveillance programme is not only related to the number of veterinarians, but also to the quality of veterinary workforce, along with the perception of farmers of disease prevention and control practices. Indeed, farmers did not regard PTB control as a "hot topic" in communications with their herd veterinarian and other farmers (Ritter *et al.* 2016).

Lastly, although the wildlife status was not considered in the model building process, it is worth to mention that the circulation of MAP in wild animals might have consequences for the livestock sector since spillover and endemicity were described in wildlife in some countries (Carta *et al.* 2013). Indeed, there is evidence of an association between the persistence of PTB in livestock and MAP-infected sympatric wildlife (Shaughnessy *et al.* 2013). Despite this, given the extremely high numbers of MAP shed by clinically infected cattle in dairy herds, wildlife could be considered to have a marginal role in the disease maintenance.

Conclusions

This study is intended to provide a comprehensive overview overview of the PTB reporting at European level over the last 24 years. This is also one of the few available studies that uses official information provided by the NVS to the WOAH (Cárdenas *et al.* 2019, Fanelli *et al.* 2021, Fanelli and Tizzani 2020, Meske *et al.* 2021).

The data used have some limitations due to transparency, diagnostic capacity and accuracy of the information provided by the countries. Additionally, it provides only information on disease status (presence or absence) without including information on the number of cases reported at country level. However, this type of information is not easily accessible through public databases.

PTB is found worldwide, causing significant losses to the agricultural industry through reduced production and compromised animal welfare. Considering the currently available diagnostic options as well as the high prevalence of PTB, it has been accepted that there is no simple solution to eradicate the disease. Nevertheless, government funding and transparency of reporting are essential for long-term prevention and control activities. Transparency not only provides information needed to control a disease, but it also influences the process of decision making and priority setting. We consider that reporting information on PTB to WOAH is of pivotal importance to provide an accurate picture of the international epidemiological situation of the disease. Not only does this study provide useful epidemiological information on PTB for decision makers, but it also highlights geographic areas with gaps in international disease reporting. In this perspective, the quality of reporting could be improved providing a clear case definition of PTB in the Terrestrial Code and enhancing surveillance activities at country level.

Data statement

The data that support the findings of this study are available on the World Animal Health Information Database (WOAH-WAHIS) Interface: https://wahis.woah.org/#/home.

References

Akaike H. 1973. Information theory and an extension of the maximum likelihood principle. *In* Proceedings of the 2nd International Symposium on Information Theory (B.N. Petrov & F. Csaki, eds). Akadémiai Kiadó, Budapest, 267-281.

Cáceres P., Awada L., Barboza P., Lopez-Gatell H. & Tizzani P. 2017. The World Organisation for Animal Health and the World Health Organization: intergovernmental disease information and reporting systems and their role in early warning. *Rev Sci Tech Off Int Epiz*, **36**, 539-548.

Cárdenas L., Awada L., Tizzani P., Cáceres P. & Casal J. 2019. Characterization and evolution of countries affected by bovine brucellosis (1996-2014). *Transbound Emerg Dis*, **66**, 1280-1290.

Carta T., Álvarez J., Pérez de la Lastra J.M. & Gortázar C. 2013. Wildlife and paratuberculosis: a review. *Res Vet Sci*, **94**, 191-197.

Dufour B., Pouillot R. & Durand B. 2004. A cost/benefit study of paratuberculosis certification in French cattle herds. *Vet Res*, **35**, 69-81.

Fanelli A., Buonavoglia D., Martinez Carrasco Pleite P. & Tizzani P. 2020a. Paratuberculosis at European scale: an overview from 2010 to 2017. *Vet Ital*, **56**, 13-21. doi:10.12834/VetIt.1829.9692.3.

Fanelli A., Tizzani P., Ferroglio E. & Belleau E. 2020b. *Cheilospirura hamulosa* in the Rock Partridge (*Alectoris graeca saxatilis*): epidemiological patterns and prediction of parasite distribution in France. *Diversity*, **12**, 484. https://doi.org/10.3390/d12120484.

Fanelli A., Trotta A., Bono F., Corrente M. & Buonavoglia D. 2020c. Seroprevalence of *Coxiella burnetii* in dairy cattle and buffalo from Southern Italy. *Vet Ital*, **56**, 193-197. doi:10.12834/VetIt.2321.13237.1.

Fanelli A. & Tizzani P. 2020. Spatial and temporal analysis of varroosis from 2005 to 2018. *Res Vet Sci*, **131**, 215-221. https://doi.org/10.1016/j.rvsc.2020.04.017.

Fanelli A., Tizzani P. & Buonavoglia D. 2021. Crimean-Congo hemorrhagic fever (CCHF) in animals: global characterization and evolution from 2006 to 2019. *Transbound Emerg Dis*, **69** (3), 1556-1567. https://doi.org/10.1111/tbed.14120.

Food and Agricultural Organization of the United Nations. 2020. FAOSTAT. (http://www.fao.org/faostat/en/#home).

Gamberale F., Pietrella G., Sala M., Scaramella P., Puccica S. & Antognetti V. 2019. Management of *Mycobacterium avium* subsp. *paratuberculosis* in dairy farms: selection and evaluation of different DNA extraction methods from bovine and buffaloes milk and colostrum for the establishment of a safe colostrum farm bank. *Microbiologyopen*, **8**, 8,e875.

Garcia A.B. & Shalloo L. 2015. Invited review: the economic impact and control of paratuberculosis in cattle. *J Dairy Sci*, **98**, 5019-5039.

Gontero C., Fanelli A., Zanet S., Meneguz P.G. & Tizzani P. 2020. Exotic species and autochthonous parasites: *Trichostrongylus retortaeformis* in Eastern Cottontail. *Life*, **10**, 31. https://doi.org/10.3390/life10040031.

Groenendaal H., Nielen M., Jalvingh A.W., Horst S.H., Galligan D.T. & Hesselink J.W. 2002. A simulation of Johne's disease control. *Prev Vet Med*, **54**, 225-245.

Harrell F. 1986. The Phglm procedure. *In* SAS Supplemental Library User's Guide, Version 5. Cary, NC, SAS Institute Inc.

Hruska K., Slana I., Kralik P. & Pavlik I. 2011. *Mycobacterium avium* subs. *paratuberculosis* in powdered infant milk: F57 competitive real time PCR. *Veterinarni Medicina*, **56**, (5), 226-230.

Humphry R., Stott A.W., Jones G.M. & Gunn G.J. 2001. An economic evaluation of Johne's disease (paratuberculosis) in the beef herd using the Markov chain model. *In* Assessment of surveillance and control of Johne's disease in farm animals in GB (G.J. Caldow & G. Gunn, eds). SAC, Edinburgh, 67-82.

Kleinbaum D.G. 1996. The Cox proportional hazards model and its characteristics. *In* Survival analysis. Springer New York, 83-128.

Koets A.P., Eda S. & Sreevatsan S. 2015. The within host dynamics of *Mycobacterium avium* ssp. *paratuberculosis* infection in cattle: where time and place matter Modeling Johne's disease. *Vet Res*, **46**, 61.

Kudahl A., Nielsen S.S. & Oestergaard S. 2011. Strategies for time of culling in control of paratuberculosis in dairy herds. *J Dairy Sci*, **94**, 3824-3834.

Luini M., Foglia E., Andreoli G., Tamba M. & Arrigoni N. 2013. Control and certification plan for bovine paratuberculosis of cattle: criteria and cost-benefit analysis | Piano di controllo e certificazione per la paratubercolosi bovina: criteri e analisi costo-beneficio. *Large Anim Rev*, **19**, 257-265.

Manning E.J.B. & Collins M.T. 2001. *Mycobacterium avium* subsp. *paratuberculosis*: pathogen, pathogenesis and diagnosis. *Rev sci tech Off int Epiz*, **20**, 133-150.

Meske M., Fanelli A., Rocha F., Awada L., Caceres Soto P., Mapitse N. & Tizzani P. 2021. Evolution of rabies in South America and inter-species dynamics (2009-2018). *Trop Med Infect Dis*, **6**, 98. https://doi.org/10.3390/tropicalmed6020098.

McNees A.L., Markesich D., Zayyani N.R. & Graham D.Y. 2015. *Mycobacterium paratuberculosis* as a cause of crohn's disease. *Expert Rev Gastroenterol Hepatol*, **9**, 1523-1534.

Nielsen S.S. 2009. The 10th International colloquium on paratuberculosis. *In* Programmes on paratuberculosis in Europe Minneapolis, Minnesota, USA, 101-108.

Nielsen S.S. & Toft N. 2009. A review of prevalences of paratuberculosis in farmed animals in Europe. *Prev Vet Med*, **88**, 1-14.

Office International des Epizooties (OIE). 2020a. Handistatus interface: Animal Health Data (prior to 2005). http://web.oie.int/hs2/report.asp?lang=en (Accessed on 22 December 2021).

Office International des Epizooties (OIE). 2018. Paratuberculosis (Johne's Disease). *In* The Manual of Diagnostic Tests and Vaccines for Terrestrial Animals (Office International des Epizooties, ed). Paris (France), 544-559.

Office International des Epizooties (OIE). 2020b. World animal health information database (WAHIS) interface. https://www.oie.int/wahis_2/public/wahid.php/Wahidhome/Home (Accessed on 22 December 2021).

QGIS Development Team. 2017. QGIS Geographic Information System. Open Source Geospatial Foundation.

R Core Team. 2018. A language and environment for statistical computing. R Foundation for Statistical Computing.

Ritter C., Jansen J., Roth K., Kastelic J.P., Adams C.L. & Barkema H.W. 2016. Dairy farmers' perceptions toward the implementation of on-farm Johne's disease prevention and control strategies. *J Dairy Sci*, **99**, 9114-9125.

Savova T., Petkov I., Dimitrova A., Petrova R., Manov V. & Lalkovski N. 2016. First case of paratuberculosis in cattle in Bulgaria, established by modern diagnostic methods. *Bulg J Anim Husb*, **3-6**, 172-178.

Schoenfeld D. 1982. Partial residuals for the proportional hazards regression model. *Biometrika*, **69**, 239-241.

Shaughnessy L.J., Smith L.A., Evans J., Anderson D., Caldow G. & Marion G. 2013. High prevalence of paratuberculosis in rabbits is associated with difficulties in controlling the disease in cattle. *Vet J*, **198**, 267-270.

Stott A.W., Jones G.M., Humphry R.W. & Gunn G.J. 2005. Financial incentive to control paratuberculosis (Johne's disease) on dairy farms in the United Kingdom. *Vet Rec*, **156**, 825-831.

Therneau T. 2020. A package for survival analysis in R. R Packag version 32-3.

Tizzani P., Fanelli A., Negri E., Silvano F., Menzano A. & Molinar Min A. 2020. Haemoparasites in red-legged partridge (*Alectoris rufa*): first record of *Haemoproteus* sp. in Italy? *J Parasit Dis*, **44**, 462-466. https://doi.org/10.1007/s12639-020-01211-x.

Vidić B., Grgić Ž., Jovičin M., Rašić Z., Savić S. & Vidić V. 2014. Prevalence of paratuberculosis infection in sheep. *Vet Glas*, **68**, 165-174.

Weber M.F., van Roermund H.J.W., Vernooij J.C.M., Kalis C.H.J. & Stegeman J.A. 2006. Cattle transfers between herds under paratuberculosis surveillance in The Netherlands are not random. *Prev Vet Med*, **76**, 222-236.

Whittington R., Donat K., Weber M.F., Kelton D., Nielsen S.S. & Eisenberg S. 2019. Control of paratuberculosis: who, why and how. A review of 48 countries. *BMC Vet Res*, **15**, 198.