Received: 5 September 2023 | Accepted: 22 October 2023

DOI: 10.1111/rda.14501

Reproduction in Domestic Animals WILEY

ORIGINAL ARTICLE

Bovine congenital defects recorded by veterinary practitioners

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Abstract

A mobile phone app was used by 59 veterinary practitioners to collect case histories and images of 191 cattle with congenital defects distributed nationally over a 3-year period. The majority of cases were recorded during the spring calving season (57.6%) in pluriparous dairy dams. The majority of calves were recorded at birth or within the first week (66.5%) in singletons born at full-term. On the majority of farms (75.9%), this was the only congenitally deformed bovine recorded up to that point in the year and on the majority of farms, there were no congenitally deformed cattle recorded in the previous 5 years. The majority of congenital defects (83.5%) were recorded in the musculoskeletal or digestive systems. The three most commonly recorded individual defects were intestinal atresia (24.1%), schistosomus reflexus (20.4%) and ankylosis (6.8%); multiple defects were recorded in 13.1% of cases. These findings highlight the relatively high prevalence of intestinal atresia and schistosomus reflexus in calves attended by veterinary practitioners, which warrants implementation of preventive measures. The project highlights the potential benefits of veterinary-practitioner apps to detect changing trends in endemic, or the emergence of novel, congenital or other conditions.

KEYWORDS
congenital defects, intestinal atresia, schistosomus reflexus, veterinary practitioners

1 | INTRODUCTION

Congenital defects may be defined as abnormalities of structure and function present at birth (Mee, 2021; WHO, 2009) but which may not be recognized in some cases until animals are older (Berry et al., 2022). They are reported to occur at a low frequency (<1%) in cattle (Bähr & Distl, 2005; Leipold & Dennis, 1993) but are under-diagnosed due to submission and reporting biases in (passive) surveillance programmes. Defects are usually classified by the body system primarily affected though in some cases multiple body systems are involved. They occur individually or combined with other defects in syndromic or non-syndromic phenotypes. The organ system most commonly reported as affected in calves is the musculoskeletal system (Aksoy et al., 2006; Sanchez-Miguel & Holmes, 2016) and the most frequent defect in this system is arthrogryposis. The causes of congenital defects may be classified as genetic, non-genetic (toxic, nutritional, infectious and physical), interactions between these two and idiopathic. In the majority of congenital defects, the cause is unknown, though this is changing with modern molecular biology techniques.

Congenital defects may be recorded by farmers, their veterinary practitioners, veterinary pathologists (in routine diagnostic or academic laboratories) and geneticists (in breeding organizations). Of these sources, the majority of scientific publications are written by veterinary pathologists and geneticists. This may bias the literature on this topic as the caseload presented to these two groups may differ substantially from the cases presented to farmers and to veterinary practitioners. This has potential implications

for our knowledge on the epidemiology, incidence, typology, aetiology and relative importance of individual congenital defects and of congenital defects compared to other disorders/diseases of food animals. This issue of submission bias is not commonly discussed in publications on bovine congenital defects; hence its real implications are unknown. It may be of particular importance when using the (potentially biased) information gathered on congenital defects to prioritize preventive/control strategies for particular defects.

One of the perspectives on congenital defects rarely documented is that of veterinary practitioners, apart from cases/case series. Veterinary practitioners are uniquely placed to detect congenital defects first-hand on farms and to provide a high quality professional diagnosis. In order to determine the potential for veterinary practitioners to contribute to surveillance of congenital defects, a nation-wide study was set up with the largest veterinary practice group in Ireland. The objective of the project was to field test a mobile phone app designed for use by veterinary practitioners to collect clinical case data during routine farm visits.

2 | MATERIALS AND METHODS

2.1 | Data and image collection

This study was set up by MC and DM within XLVets Ireland, the largest veterinary practice group in Ireland for application by the veterinary practitioners within its 50 practices. A 15-question questionnaire (Appendix S1) was designed, piloted with veterinary practitioners, and then formatted as a mobile phone app using Typeform (www.typeform.com). In addition, up to three photographic images or videos could be recorded per case. The app was provided to all veterinary practitioners in the practice group ($n = 190$) in December, 2020. The results reported here came from the initial 3 years (2021–2023) of the study. Epidemiological information and images were collected during routine farm visits (mainly calvings). Necropsy examinations were generally not conducted by veterinary practitioners on cases with congenital defects. The questionnaire data and the images were stored in a secure Azure cloud server and presented as an interrogatable dashboard using Microsoft Power Bi.

2.2 | Data and image analysis

The data from the questionnaires and the links to the images were downloaded into Excel for analysis. Duplicate records, records of congenital defects in other species (sheep) and records of non-congenital defects were deleted. Individual cases were categorized by the body system/s affected. All 191 cases were reviewed by the first author using the case history and images and this diagnosis was compared with those of the veterinary practitioners. For cases ($n = 10$) where the defect classification was unclear, these were sent for independent review by five external subject matter experts (SMEs). The final reviewed case classification was compared with the original veterinary practitioner classification. Throughout the results, unless otherwise stated, the original veterinary practitioner case classification was used.

2.3 | Ethics exemption

This study collected no personal or sensitive information, there were no animal experimental studies and all information was de-identified in the data management process and so met the criteria for a low-risk study reporting no personal participant or animal experimental data.

3 | RESULTS

3.1 | Epidemiological information

In total, 59 vets in 28 XLVets Ireland veterinary practices distributed nationally across 19 of the 26 Irish counties participated in the project (Figure 1). The number of cases/vet and/practice varied between 1 and 23 and 1 and 43 respectively. The questionnaire took, on average, 5 min 18 s to complete.

The number of cases/year declined over time; 2021 ($n = 90$), 2022 (71) and 2023 (30); in total, 191 cases. The majority of cases (57.6%) were recorded during the spring calving season (January–March; 110). The number of cases/county varied between 1 (Laois, Monaghan) and 39 (Tipperary) with the majority of cases recorded in the province of Munster (143) and the remainder in Connacht (24), Leinster (17) and Ulster (7).

The majority of dams were of a dairy breed (138), with the remainder beef (48), dual-purpose (4) or unknown (1). The most common dam breeds were Holstein Friesian/cross (132), Limousin/cross (22) or Charolais/cross (10); 13 dam breeds were recorded. The majority of sires were of a beef breed (93), with the remainder dairy (81), dual-purpose (2) or unknown (15). The most common sire breeds were Holstein Friesian/cross (81), Aberdeen Angus (33) or Limousin (20); 11 sire breeds were recorded. The majority of cows were bred by artificial insemination (77), with the remainder by natural service (53), embryo transfer (2) or unknown (59). The majority of dams were pluriparous (141), with the remainder primiparae (24) or unknown (26).

There was a similar number of male (43) and female cases (42) recorded, but the majority of cases had an unrecorded sex (106). The majority of cases were singletons (178) with the remainder twins (13). Gestation was full-term in the majority of cases (180) with the remainder premature (8) or overdue (3). The majority of cases were assisted at calving (Caesarean section [46], non-surgical assistance [41] or foetotomy [20]) with the remainder unassisted at calving (84). The majority of cases were recorded at birth (76) with the remainder in the first day (21), days 2–7 (30), older (up to 2 years of age) (9) or unknown (55).

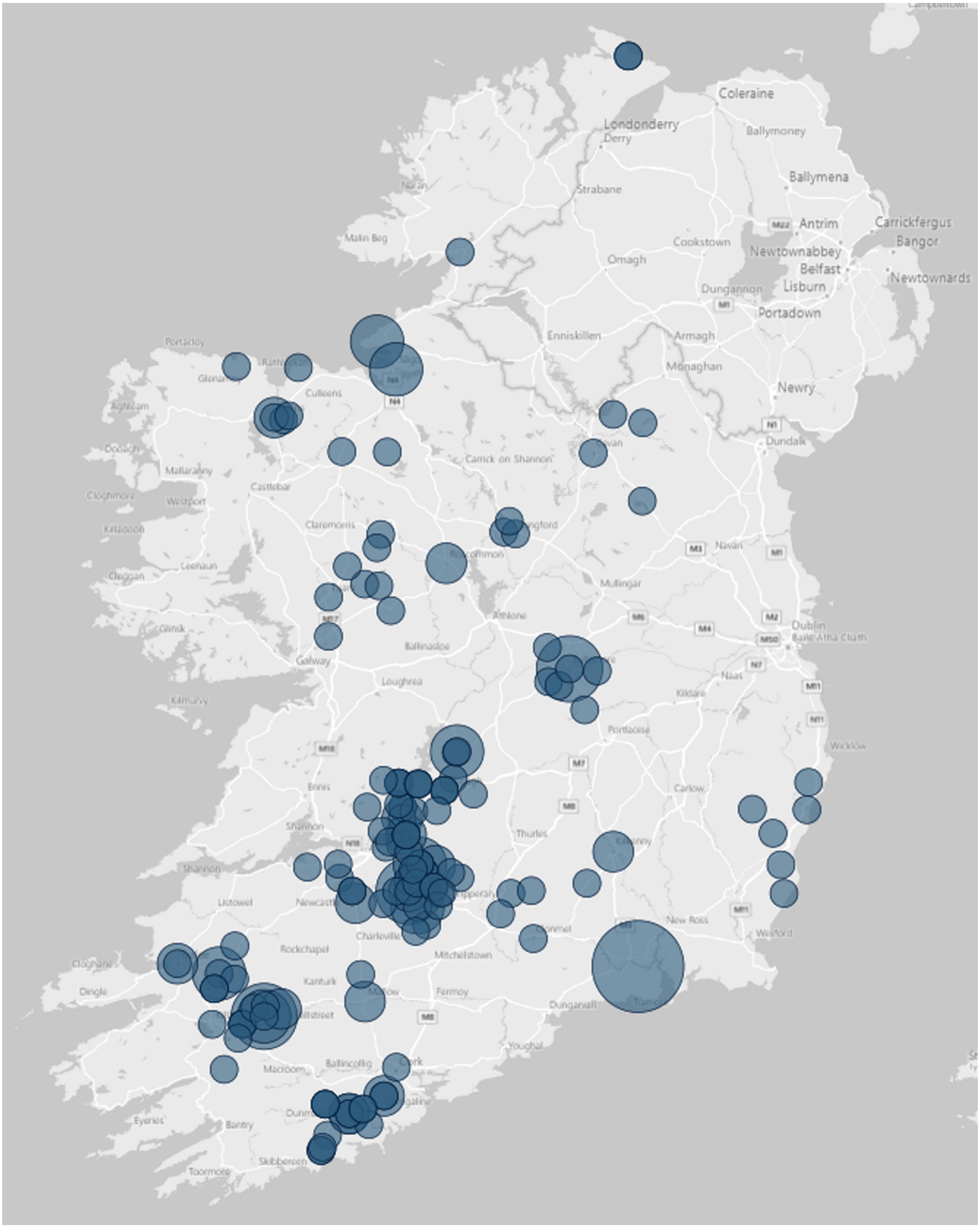

FIGURE 1 Locations of herds containing cattle ($n = 191$) with congenital defects in the Republic of Ireland recorded by veterinary practitioners (2021–2023); circle size indicates number of cases/practice.

On the majority of farms (75.9%), this was the only congenitally deformed bovine recorded up to that point in the year (145) with the remaining farmers recording multiple previous cases (21) or unknown (25). On most farms (47.6%), there were no congenitally deformed cattle recorded in the previous 5 years (91) with the remaining farmers recording one case (55), multiple cases (23) or unknown (22).

3.2 | Congenital defect information

As the data in Table 1 show, the majority of cases (83.5%) were recorded in the musculoskeletal or digestive systems. The cases involving multiple body systems most commonly affected the musculoskeletal and one or more body systems (10/16 cases).

The types of congenital defects recorded by veterinary practitioners are shown in Table 2. The three most commonly recorded individual defects were intestinal atresia (24.1%), schistosomus reflexus (20.4%) and ankylosis (6.8%); multiple defects were recorded in 13.1% of cases. Intestinal atresia included atresia of the intestines (43) and atresia ani (3). Multiple defects most commonly affected the musculoskeletal system (22/25 cases) and of these, those involving ankyloses (11) and palatoschisis (6) were the most common.

The 46 cases of intestinal atresia (Figure 2) were reported by 22 practitioners from 17 practices in 12 counties. The predominant dam type was dairy (33) and of Holstein Friesian breed (33), but while the predominant sire type was beef (23)—the most common single sire breed was Holstein Friesian (17). Most of the dams were bred by natural service (15) or AI (14) with many cases not recorded (17). The dams were mainly pluriparae (36); one was primiparous and nine unrecorded. All the calves were singletons born at full-term (45) or over-term (1). Calf sex was only recorded in 18 cases of which 11 were male and seven female.

The 40 cases of schistosomus reflexus (39 single defect and one case with hydrocephalus) (Figure 3) were reported by 26 practitioners from 20 practices in 12 counties. The predominant dam type was dairy (31) and of Holstein Friesian breed (28) as was the predominant sire type (20) and breed (20). Most of the dams were bred by AI (15) or natural service (10) with many cases not recorded (15). The dams were mainly pluriparae (30); five were primiparae and five unrecorded. The majority of calves were singletons (37) and the remainder twins (3) with unaffected co-twins, born at full-term (38) or premature (2). Calf sex was only recorded in 11 cases of which seven were female and four male.

The comparison between the diagnoses of the veterinary practitioners and the first author is shown in Table 3. When cases without

TABLE 1 Body systems affected by congenital defects in 191 cattle as recorded by veterinary practitioners, in descending order.

Body system	No. of cattle (%)
Musculoskeletal	103 (53.9)
Digestive	47 (29.6)
Multiple	16 (8.4)
Neurological	8 (4.2)
Ophthalmic	5 (2.6)
Not recorded	4 (2.1)
Urogenital	3 (1.6)
Integumentary	3 (1.6)
Cardiovascular	2 (1.1)

TABLE 2 Congenital defects recorded in 191 cattle by veterinary practitioners, in descending order.

Congenital defect	No. of cattle
Intestinal atresia	46
Schistosomus reflexus	39
Multiple defects	25
Ankylosis	13
Cleft face/muzzle/palate	11
Conjoined twins/dicephalus	5
Umbilical hernia	4
Anury/short tail	3
Cataracts	3
Meningocoele	3
Omphalocoele	3
Hydrocephalus	3
Amorphus globosus	3
Contracted tendons	2
Dwarf	2
Anophthalmia/microphthalmia	2
Spina bifida	2
Ventricular septal defect	2
Deformed hind legs	2
Alopecia/hypotrichosis	2
Anasarca	1
Brachycephaly	1
Forelimb polymelia	1
Cranial 'wart'	1
Hindquarter continuous tremor	1
Lumbar spinal abnormality	1
Swollen abdomen	1
Bilateral shoulder and hip luxation	1
Forelimb amelia	1
Perosomus elumbis	1
Omphallorhagia	1
Polycystic kidneys	1
Subcutaneous shoulder/cervical mass	1
Long ano-genital distance (AGD)	1
Cloaca	1
Unknown	2

FIGURE 2 Intestinal atresia was the single most commonly diagnosed congenital defect in calves by veterinary practitioners (Photo courtesy of Tadhg Gavin, Killaloe Vets).

FIGURE 3 Schistosomus reflexus was the second most commonly diagnosed congenital defect in calves by veterinary practitioners (Photo courtesy of K. O'Sullivan, Glasslyn Veterinary Clinic).

images or with unclear images are excluded ($n = 91$), a consensual diagnosis was reached in 90% of 100 cases.

The 10 non-consensual diagnosis cases in Table 3 are listed in Table 4. In most of these cases, the differences in diagnoses are in detail of the descriptor terms utilized for a deformed animal.

The diagnoses in the 10 separate cases where the defect classification was unclear to first author, which were reviewed by five SMEs are shown in Table 5. In seven of the 10 cases, multiple differential diagnoses were suggested.

4 | DISCUSSION

This study found that the body system most commonly affected by congenital defects was the musculoskeletal system and that the three most common defect categories were intestinal atresia, schistosomus reflexus and multiple defects. Defects varied in severity from a short tail to the most severe congenital defect, amorphous globosus (Mee, 1990).

The finding that the musculoskeletal system was the body system most commonly affected by congenital defects (Table 1) was in agreement with previous reports (Aksoy et al., 2006; Sanchez-Miguel & Holmes, 2016). However, the finding that schistosomus reflexus was the most common musculoskeletal defect and the second most common overall defect was surprising. Schistosomus reflexus is generally considered a rare, sporadic congenital defect about which many cases/case series have been published (e.g. Cavalieri & Farin, 1999; Nicolae et al., 2020). By combining the data from this study (40 cases) with the four largest published case series (Kemp, 2021—15 cases in Wales; Hoda et al., 2018—35 cases in Bangladesh; Čítek, 2012—29 cases in the Czech Republic and Knight, 1996—90 cases in Australia), it is possible to present epidemiological details on the largest combined database of schistosomus reflexus; 209 cases. The majority of these 209 cases were singleton (92%) females (54%) delivered by caesarean section or foetotomy (85%) in pluriparae (79%) of a dairy breed (79%). Apart from the delivery method, the other factors were considered to represent normal background frequency

distributions by the various authors. The most recent estimates of the prevalence of schistosomus reflexus indicate that approximately 0.01% (1:10,000) of live, aborted and stillborn calves are affected (J. F. Mee, unpublished) or 0.62%–1.3% of veterinary-assisted dystocia (Kemp, 2021; Knight, 1996); <1% of sires produce an affected calf (Čítek, 2012). Schistosomus reflexus is never ranked as one of the most commonly diagnosed defects. This ranking here reflects the primary presenting clinical effect of schistosomus reflexus—veterinary-assisted dystocia. This is borne out by the high frequency of caesarean sections and foetotomies (93%) needed to deliver these calves (all of which were assisted). This puts a new perspective on this lethal defect. It is an important cause of veterinary-assisted dystocia with the associated economic and welfare sequelae. This suggests that preventive/ameliorative measures are warranted. Traditionally, schistosomus reflexus has been thought to be an autosomal-recessive inherited trait (Čítek, 2012), however, the latest research suggests that a simple recessive inheritance is unlikely and that there is evidence of heterogenic causality by spontaneous de novo mutations (Jacinto et al., 2022). Given this lack of consensus about aetiology, it may be prudent to recommend in affected herds that when cows are scanned approximately 60 days after service, the conceptus is examined more closely for potential abnormalities and if detected (Figure 4), such cases can be aborted (prostaglandin F2a) or recorded for closer parturient supervision, including potentially elective caesarean section. Schistosomus reflexus is reported to be the most easily detectable foetal anomaly during ultrasonographic pregnancy examination in cattle (DesCoteaux et al., 2010).

The finding that the digestive system was the second most commonly affected body system (Table 1) was not unexpected. However, the finding that intestinal atresia was the most common overall defect was surprising. The most commonly diagnosed bovine congenital defect has variously been attributed to umbilical hernia (Čítek

TABLE 3 Comparison of diagnostic categories of congenital defects in 191 cattle by veterinary practitioners on farm and by the first author based on anamnesis and images.

Diagnostic category	No. (%)
Consensual diagnosis	90 (47.1)
No images	81 (42.4)
Unclear images	10 (5.2)
Dissensual diagnoses	10 (5.2)

TABLE 4 Comparison of non-consensual diagnoses of congenital defects in 10 cattle by veterinary practitioners on farm and by first author based on anamnesis and images.

Veterinary practitioners' diagnoses	First author diagnoses
Ankylosis (3)	Perosomus elumbis (1), Ankylosis/Torticollis (2)
Ankylosis/Cleft palate/Craniocele (1)	Ankylosis/Cleft palate/Hydrocephalus (internal) (1)
Brachygnathia/Cleft palate (1)	Macrostomia/Cleft palate (1)
Dicephaly (1)	Thoracopagus conjoined twins (1)
Foetal monster (1)	Foetal gigantism
Meningocele (1)	Hydrocephalus (internal) (1)
Schistosomus (1)	Perosomus elumbis (1)
Spina bifida/Myelomeningocele/Arthrogryposis (1)	Spina bifida/Perosomus elumbis (1)

TABLE 5 Comparison of diagnoses of congenital defects in 10 cattle by veterinary practitioners on farm and by five SMEs based on anamnesis and images.

Veterinary practitioners' diagnoses	SMEs' diagnoses
Ankylosis/localized skin missing	Localized cutaneous aplasia, epitheliogenesis imperfecta/aplasia cutis, epidermiolysis bullosa, Ehler–Danlos syndrome
Brachynathia/deformed jaw	Brachygnathia/oral hamartoma, Palatoschisis/bilateral cleft lip, jaw and palate
Cranial wart-like structure	Congenital cutaneous hamartoma
Cloaca?	Cloaca and vitelline fistula
Foetal monster	Gigantism of prolonged pregnancy and spontaneous large offspring syndrome (SLOS)
Hindquarter spasms	BVDv-induced hypomyelogenesis, Charcot–Marie–Tooth disease, inherited congenital hypomyelinogenesis and myotonic dystrophy
Luxated hips and shoulders	Congenital dysmyelogenesis, vertebral column deformity, manganese deficiency, trauma and chondrodysplasia
Mass over ribs and neck	Choristoma, teratoma, infiltrative lipoma, congenital thymoma and thymic lymphoma
Meningocele	Cerebral hypoplasia
Schistosomus	Schistosomus

FIGURE 4 Schistosomus reflexus can be diagnosed using transrectal ultrasonography approximately 60 days after service (Image courtesy of G. Gnemmi, BovineVet).

et al., 2009) or arthrogryposis (Bähr & Distl, 2005). The only Irish studies conducted on intestinal atresia have estimated that it occurs in 0.3%–0.4% of all dairy calves born and in up to 25% of herds (Keane et al., 2023; Mee, 1994). The top ranking of atresia in this study reflects its two common clinical presentations, veterinary-assisted dystocia and a call out to examine/kill a calf that has become anorexic, bloated, in pain and is not passing faeces. Again, this highlights both the economic costs to the farmer and the welfare costs to the cow and her calf associated with this common bovine congenital defect. While the number of cases of intestinal atresia recorded here was limited, it did suggest that calves from pluriparae and males were more commonly affected. These trends are borne out by a recent Irish study of 197 cases which found that both pluriparity and male gender were significant risk factors (Keane et al., 2023). As with schistosomus reflexus, this indicates that preventive measures are warranted at a national/supra-national level. However, the aetiology of intestinal atresia in cattle is unclear. Partly, this may be due to the 'noisy' phenotype; atresia may occur in the duodenum, jejunum, ileum, colon or anus; it may occur at one or multiple locations in the intestinal tract; and it may be classified into at least three different morphological types (van der Gaag & Tibboel, 1980). This presents challenges when trying to diagnose the aetiology as if there are multiple phenotypes, there may be multiple causes. Recently, a genetic basis for 'all type atresia' was established for Irish Holstein Friesian and Jersey cattle (Keane et al., 2023). This has previously been documented for Holstein Friesian (Syed & Shanks, 1992) and Swedish Highland cattle (Nihleen & Eriksson, 1958). While an alternative hypothesis of attritional early pregnancy detection has been proposed (Brenner & Orgad, 2003), this has also been refuted (Romano et al., 2016). Given the relative importance of intestinal atresia in cattle, it is suggested that both the phenotype and the genotype of all reported cases should be recorded nationally and appropriate breeding policies adopted based on the findings.

The third most commonly affected body system category was multiple body systems and this was also the third most commonly diagnosed defect category (Tables 1 and 2). Multiple defects may occur syndromically (e.g. arthrogryposis-hydranencephaly syndrome [AHS]) or non-syndromically, where random defects co-occur. While the latter may represent random de novo mutations, the former usually have a single cause, for example, a viral teratogen such as Schmallenberg virus causing AHS (Collins et al., 2019). In cases where multiple body systems were affected in this study, the musculoskeletal system was most commonly involved, most commonly with the neurological system, though multiple other body systems were co-affected suggesting non-syndromic occurrence. Similarly, in cases where multiple defects were diagnosed, defects of the musculoskeletal system were most commonly detected and within these, ankylosis and palatoschisis were most frequent, though with multiple combinations of other defects indicating their non-syndromic nature. These findings suggest that the cases with multiple defects diagnosed here did not have a unified aetiology and were more likely due to random de novo mutations of unknown origin.

An encouraging and novel finding from the study was the high level agreement between the diagnoses of the veterinary practitioners and the external auditors; first author and the five SMEs. In the 10% of the 191 cases where the veterinary practitioners and the first author disagreed, it was primarily about the descriptors used to define a case rather than the defect per se. Of the 10 cases where the classification was unclear to the first author, the SMEs proffered multiple diagnoses in seven of these cases indicating that a diagnosis could not definitively be established from the case history and accompanying image/s. These results suggest that in general, veterinary practitioners had a high level of knowledge of bovine congenital defects but that in a small number of cases, it is not possible to make a definitive diagnosis, even after consulting SMEs, using the app recording method.

The epidemiology of the cases in this study largely reflect the prevailing management, breed structure and geolocation of cattle farming in Ireland. Thus, the majority of cases were recorded at birth and in the spring, reflecting the seasonal nature of calving in Ireland. The preponderance of cases in Munster also reflects the high cattle herd density and numbers in this province. The prominence of dairy breed cases, in particular Holstein Friesian, also reflects the prominence of this breed nationally. At variance with typical cattle management was the high prevalence of caesarean section and foetotomies in the data set; this reflects the high incidence of veterinary-assisted dystocia associated with particular deformities, in particular schistosomus reflexus and other musculoskeletal deformities. The sporadic nature of most of the defects is highlighted by the majority of farmers reporting that they had no previous cases in the year the first defect was recorded and that they had no defects in the previous 5 years either. Comparable published epidemiological data are difficult to find but

similar conclusions were drawn by Knight (1996) when discussing a longitudinal study of schistosomus reflexus.

Despite the novelty of this study, it had some limitations. In the majority of cases, the diagnosis was not confirmed by necropsy; however, in many cases, this was unnecessary, for example, schistosomus reflexus and in all cases diagnoses were made by veterinarians. Cases reported were primarily those diagnosable from external visual inspection, hence, the very limited number of cases involving certain internal organs that are commonly reported in the literature, for example, cardiac defects (Caivano et al., 2023). Whether practitioners recorded all congenital defect cases they observed or only a sample and how they might have selected this sample was unknown. Not all cases were accompanied by images (photographs/videos) to assist diagnosis, and of those that were, some were of insufficient quality to add diagnostic information. This could be improved by adding a no image bypass edict to the app and guidelines on how to collect better quality images. Similarly, data were frequently missing from the case history, especially case age and sex and total number of calves born to date, which reduced the quality of the epidemiological information. The absence of necropsy information and samples, the missing case history information and the missing/poor quality images probably contributed to the unclear diagnoses in a small number of cases. However, despite these limitations, good quality phenotypic diagnoses were achieved by practitioners in the majority of cases.

As a proof-of-concept study, this research established that the app was a convenient tool for busy veterinary practitioners to use to collect useful information on bovine congenital defects which can be used to generate an annotated photo-archive suitable for peer-education. The project also highlights the potential of veterinary-practitioner apps to detect changing trends in endemic, or the emergence of novel, congenital conditions. The Schmallenberg virus outbreak emphasized the importance of veterinary practitioner surveillance. With the launch of the National Genotyping Programme in 2023, Ireland is planning to be the first country in the world to genotype its entire national cattle herd. Sharp phenotypes of abnormal cattle, as produced here will contribute significantly to this programme. This veterinary-practitioner-led data-recording model is also latent with possibilities for use in participatory epidemiology (PE) (Chenais & Fischer, 2021) across other clinically relevant conditions for farmers.

Following completion of this pilot project, a re-evaluation of the questionnaire has highlighted potential improvements to reduce missing data (no by-pass answer edict) and improve data (more precise question wording) and image quality (specific image collection protocol).

5 | CONCLUSIONS

This study highlighted two congenital defects of cattle which are often considered as sporadic in occurrence and of low prevalence. Based on the findings reported here, both intestinal atresia and schistosomus reflexus need to be viewed in a new light as clinically important bovine congenital defects warranting preventive strategies at farm and national levels. The results of this study also indicate that veterinary practitioner surveillance using mobile phone apps could be expanded to include other clinically important conditions and in other countries.

AUTHOR CONTRIBUTIONS

MC conceptualised the study, managed the database and dashboard, and contributed to redrafting the paper. DM conceptualised the study and in conjunction with the XLVets Ireland veterinary practitioners, carried out the field work and contributed to redrafting the paper. JFM contributed to the survey methodology, analysed the data, wrote the first draft of the paper, re-edited the paper and wrote and submitted the final draft of the paper.

ACKNOWLEDGEMENTS

The authors thank the participating veterinary practitioners and their clients for collecting these case histories and images. They also thank Arcangelo Gentile and Joana Gonçalves Pontes Jacinto, University of Bologna, Italy; Cosme Sanchez Miguel, Department of Agriculture, Food and the Marine, Ireland; Rocio Rivera, University of Missouri, USA and Jørgen Agerholm, University of Copenhagen, Denmark for reviewing selected cases and Giovanni Gnemmi, BovineVet, Italy for use of his ultrasonographic image. Open access funding provided by IReL.

CONFLICT OF INTEREST STATEMENT

None of the authors have any conflict of interest to declare.

DATA AVAILABILITY STATEMENT

The data generated during the current study are available from MC upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Mee, J. F., Murphy, D., & Curran, M. (2023). Bovine congenital defects recorded by veterinary practitioners. *Reproduction in Domestic Animals*, *00*, 1–9. https://doi.org/10.1111/rda.14501