

Global perspective on bovine abortion - current prevalences, normal rates, diagnoses and aetiologies: a mini-review

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Abstract

The case definition of bovine abortion varies with the purpose of use from legislative and research to field definitions; it generally encompasses days 42–260 of gestation. This variation can affect comparisons between prevalence rates. Animal-level prevalence estimates vary between 5 and 20% (mean ~10%) while herd-levels vary between 0 and 30% in published studies. Intervention thresholds ('normal herd-level abortion rate') also vary widely from 1 to 10% depending on the case definition and the underlying region-specific abortion rate. The infectious abortion diagnosis rate globally is ~45% with *Neospora caninum* being the most commonly detected abortifacient. Thus, the majority of abortions, in particular, sporadic (not outbreak) cases, have no diagnosed cause. However, current advances in the routine application of molecular diagnostics both for pathogens and for lethal alleles is steadily reducing this diagnosis-not-reached rate.

Cattle, gestation, pregnancy loss

While it is traditional to define bovine abortion as expulsion of a dead or non-independently viable live foetus and its adnexa between ~42 and ~260 days of gestation (Mee 2023) this is a purely academic case definition. In practice many different definitions of abortion are used which reflect legislative definitions, national regulations, institutional definitions and 'field definitions' as used by practicing veterinarians and their clients. For example, in some countries abortion is combined with perinatal mortality into a portmanteau 'abortion-perinatal mortality' (APM) (Van Loo 2023). Although this differentiation may appear to be semantic, it is critical when comparing abortion prevalence rates across countries or studies within countries and in establishing benchmarks for intervention.

Our perception of bovine abortion prevalence and aetiology usually comes from the scientific literature. But the latter is biased by gross under-reporting of all (especially first and second trimester) abortions (Bronner et al. 2014) when estimating prevalence. Reported causes of under-reporting include cost and resources involved in testing (50% of 1,157 Canadian dairy farmers surveyed), no interest in testing (29%), and not being aware of the importance of testing (21%) (Denis-Robichaud et al. 2019). Similarly, passive (rather than active) surveillance sampling of the minor proportion of reported abortions actually submitted for investigation (e.g. Hayes et al. 2023) potentially biases estimated causation rates. These limitations in our methodologies should be recognised when we review our current knowledge of bovine abortions and how we attempt to reduce such losses globally.

Despite these issues, it is clear that bovine abortion can exert a considerable financial cost estimated recently at US\$ 1,415 per abortion for dairy and US\$ 440 per abortion for beef farmers (Cantón et al. 2022). Though legally all abortions must be reported and investigated in many countries, most farmers 'accept' sporadic abortions and associated costs and so do not report them (Denis-Robichaud et al. 2019). The legal imperative to report all abortion cases stems from the public health concerns associated with zoonotic

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abortifacients, e.g. *Brucella abortus*. However, from personal experience, they become more interested in investigation and prevention of financial costs once prevalence increases. But the challenge is to define when has the abortion rate become ‘too high’.

Prevalence of abortion

Before reviewing the prevalence of bovine abortion, it is instructive to background this by examining abortion rates in other farm animal species. In sheep an abortion (< 137 days) rate of 2–3% of ewes has recently been estimated (Crilly et al. 2021), in swine, an abortion (35–109 days) rate of up to 4% of sows is considered ‘normal’ (Maes et al. 2023), and in horses an abortion (70–300 days) rate of 4% has been recently recorded (Roach et al. 2021). Thus, abortion is reported to occur at a similarly low rate across our other common livestock species.

Given cattle are a herd species, we need to address bovine abortion prevalence at both animal- and herd-levels. In addition it must be recognised that loss rates are much higher in early than late pregnancy. Thus the most recent estimates of animal-level early abortion rates from meta-analyses are 9% (45–90 days) in dairy cows (Albaaj et al. 2023) and 6% (32–100 days) in beef cows (Reese et al. 2020). Estimates of animal-level full pregnancy abortion rates in dairy cows have recently been reviewed at between 5 and 20% (30–279 days), (Ealy and Seekford 2019) with an average of ~12% (42–260 days), (Wijma et al. 2022). Estimates of animal-level dairy mid-late term abortion rates are much lower varying between 1.2% (> 152 days and < 251 days), (Neupane et al. 2023) and 1.7% (120–259 days) (Mee, 1992). As expected, herd-level abortion rates vary widely, between 0 and 31%, in published studies (McDougal et al. 2005, Gadlicke and Monti 2013). It is estimated that between 5 and 10% of herds experience high (> 5%) abortion rates though this may vary with underlying base-rates. With increasing use of precision livestock farming (PLF) technologies which can monitor activity, which is altered by abortion/calving (Lin et al. 2023, Horváth A et al. 2021), it is possible detection/recording rates of (early) potential abortions will increase in future as bovine digital phenotypes are more clearly defined.

There are very few published datasets showing secular temporal trends in abortion rates though more are published on temporal trends in infectious causes of abortion (Hecker et al. 2023; Mee 2023). A recent report from the US showed a significant decline in late-term abortion rates (> 152 days) in recent years attributed to indirect genetic selection (Neupane et al. 2023). With increased use of anti-abortifacient vaccines (e.g. *Leptospira* spp.) and establishment of abortifacient eradication programmes (e.g. BVDv) internationally, it might be expected that infection-associated abortion rates would decline (Mee et al. 2023a), though infection-associated diagnosis rates may increase due to improved diagnostics.

‘Normal’ herd-level abortion rates

Given the wide variation in abortion rates at the herd-level outlined above (0–31%), farmers (and their veterinarians) need a benchmark above which the abortion rate is ‘abnormal’ and intervention, with associated costs, is warranted. However, as all outbreaks (‘abortion storms’) start with a single case, it is recommended to submit all cases for investigation, especially apparently ‘sporadic’ index cases. This breakpoint for what is ‘normal’ and hence acceptable (threshold of acceptance) and not warranting investigation may be calculated statistically or by farmer and veterinarian opinion based on their experience of pregnancy loss rates in their herds. If the former approach is adopted, one may arbitrarily use the highest percentile of herds’ abortion rate as ‘abnormal’, accepting that under-recording of actual abortion rates is common so many herds will have ‘0’ abortions right skewing

the distribution. For example, Thobokwe and Heuer (2004) found that 4% of their dairy herds had an abortion rate of > 5% whereas Clothier et al. (2020) found that 10% of dairy and 11% of beef farmers reported abortion rates of > 5%. However, in the absence of accurate data on herd-level abortion rates, the opinions of farmers and their vets are more commonly used to decide on the threshold of acceptance/intervention. This approach may yield very different thresholds in different regions/countries based on local experience of abortion rates. For example, in the UK and Ireland a recent study showed that the most commonly selected thresholds by vets (81%), dairy (55%) and beef (48%) farmers were 2–5, 2–5 and > 0%, respectively, for abortions defined as expulsion of a foetus between the size of a mouse and a small calf (Clothier et al. 2020). In contrast, an intervention level of 10% has been recommended for dairy herds in the US (Heersche 2023). Some of this large difference in herd-level abortion thresholds may be attributable to differences in underlying actual abortion rates and abortion recording rates and some to differences in the case definition of ‘abortion’ referred to above. Thus, where early abortions are included (e.g. following confirmed pregnancy at ~30-day ultrasonography examination), intervention thresholds are likely to be much higher than when abortion only includes ‘observed abortion’, usually > 120 days based on the gestational submission profile of foetuses submitted to veterinary diagnostic laboratories (Mee 2021; Van Loo 2023).

Diagnosis of abortion

The diagnosis rate of bovine abortions (in most studies this is effectively the infection-associated abortion rate) has increased over time from approximately 40% in 2000 to ~50% in 2022 with an overall diagnostic rate of 46% over this period (Hecker et al. 2023). However, these point estimates obscure the most important modifiable factor affecting diagnosis rates – number of conceptuses submitted for thorough examination; the more foetuses submitted/herd the higher the diagnosis rate (Van Loo 2023). Unfortunately for most herds only in a minority of actual abortions is the foetus (and much less commonly, the placenta) submitted.

This has implications for prioritisation of testing resources. The first conceptus submitted/herd-year should be prioritised for regulatory or zoonotic testing (e.g. for *Brucella abortus*) and any additional tests that can be conveniently carried out on the same sample (e.g. abomasal contents, placenta), for example routine bacterial/fungal cultures. However, given the low diagnosis rate in sporadic abortions, escalated testing (e.g. wider pathogen profile, routine histopathology and molecular PCR, next-generation sequencing testing) might economically be reserved for multiple/outbreak/abortion ‘storm’ events where an infectious aetiology is much more likely to be diagnosed. However, such sample triage depends on an accurate case history differentiating ‘first submitted’ from ‘first observed/occurred’.

One-off maternal post-abortion blood sampling is routinely used as a proxy for conceptual sampling when the latter is unavailable or to accompany the conceptus. In the former case it can be quite useful in predicting foetal infection status. For example, a single maternal serum sample from an unvaccinated cow can predict foetal *Salmonella* Dublin status with an accuracy of 85% (Sánchez-Miguel et al. 2018). Similarly, a *Neospora caninum*-seropositive dam serum sample warrants foetal cerebral histopathology/herd-level serology testing. Given that transporting the conceptus to a veterinary laboratory may be impractical, dam case-cohort sero-diagnosis may provide useful strong circumstantial evidence of an infectious abortifacient (e.g. *Coxiella burnetii*) in the herd (Barigye et al. 2021).

Traditional methods of abortifacient detection such as culture are being supplemented with PCR testing (now available as rapid in-house small pack units, e.g. POKKIT Central

Nucleic Acid Analyser manufactured by GeneReach) internationally for recognised abortifacients. However, recent studies on the microbiome of the pregnant uterus and of the conceptus indicate that in future next or whole genome sequencing will need to be applied to routine diagnostic samples from abortion cases (Maes et al. 2023) with the attendant challenges in interpreting site-specific microbiome profiles. Early studies using the metagenomics approach have yielded promising results in identifying pathogens undetectable with routine culture (DeLooz et al. 2015).

In addition to these conventional approaches to abortion diagnosis, alternative methodologies have recently been proposed. For example, testing for biomarkers of inflammation in foetal serum (acute phase proteins, APPs) may differentiate infected from non-infected aborted or stillborn foetuses (Jawor et al. 2017; Aras and Yavuz 2022). Application of metabolomics to maternal post-abortion blood samples has also been proposed as an adjunct diagnostic tool which may differentiate between infectious and non-infectious abortions using APP profiles (Gädicke et al. 2021).

Aetiology of abortion

From submitted cases (which are a biased sample of actual abortion cases) globally between 40 and 50% can be attributed to infectious abortifacients (Hecker et al. 2023; Mee 2023). The other submitted cases with a diagnosis-not-reached (DNR) may be infectious in origin but not have tested 'positive' or are non-infectious in origin, hence this is potentially a false dichotomy. Additionally, in some countries little data exists on the causes of abortion (e.g. Bariğye et al. 2021) hence it is not possible to establish the ratio of infectious to non-infectious aetiologies.

In either case, the majority of bovine abortions appear to be caused by non-infectious factors. Given this fact, it is perhaps misguided that the main focus of abortion diagnosis is on infectious, not non-infectious causes. Misguided but not surprising as determining non-infectious causes of abortion is much more challenging. While it may be possible to categorise the proximate cause of pregnancy loss as, for example, a lethal congenital defect (Mee et al. 2023b), this does not elucidate the ultimate cause. With the increasing detection of recessive lethal alleles in cases of bovine embryonic and early foetal mortality, it is likely that genetic causes contribute substantially to the aetiology of DNR-associated non-infectious abortion. The best example of mutation-associated bovine abortion is the sire Pawnee Farm Animal Chief which has been linked to over half a million abortions worldwide (Adams et al. 2016). The role of toxins, in particular, mycotoxins in bovine abortion is often proposed, and there are supportive (e.g. Kallela and Ettala 1984) and non-supportive case studies (e.g. Carlos et al. 2017) but lack of routine testing hampers elucidation of their prevalence and relevance. As modern dairy cows are pushed metabolically to achieve higher milk production, it is possible that dietary limitations and progesterone imbalances will lead to non-infectious abortions and conversely, cows on low input systems may also suffer from dietary deficiencies leading to abortion. In certain parts of the world heat stress is a physical cause of bovine abortion, particularly in Holstein cows (El-Tarabany and El-Tarabany 2015). Additionally, assisted reproductive technologies are associated with higher early abortion rates (Crowe et al. 2024). Recently, a hypothesis of environmentally-induced excess plant nitrate accumulation resulting in the formation of abiotic nanoparticles in the placenta leading to abortion outbreaks has been proposed in mares and ruminants (Swerczek and Dorton 2019).

While internationally, *Neospora caninum* is the most commonly detected pathogen in cases of bovine abortion (Mee 2023) in individual countries other pathogens may be of greater import, e.g. *Brucella abortus* in tropical and subtropical regions. The aetiology of abortion is determined by the presence/prevalence of abortifacients in the animals'

environment and the control measures adopted to prevent abortion. Thus, where certain abortifacients are being eradicated, e.g. BVDv, the infectious profile may change with more abortions caused by sporadic infections (Mee and Kenneally 2021). Most studies on the aetiology of abortion report common bacterial and fungal causes (results readily available from routine culture/PCR) and common viral causes (increasingly from PCR testing). However, there are many other less commonly tested for pathogens capable of causing abortion but which are not routinely diagnosed as such due to limited laboratory resources, difficulties in detection or lack of prioritisation of these pathogens with unclear prevalence and relevance, e.g. *Mycoplasma* (Byrne et al. 1999) and *Ureaplasma* spp., (Delooz et al. 2023), *Anaplasma phagocytophilum* (Van Loo et al. 2023) and *Chlamydia* and *Chlamydia*-like organisms (Wheelhouse et al. 2015). These ‘hard-to-reach’ pathogens may contribute, in part, to the DNR gap in our knowledge of the aetiology of bovine abortion.

Conclusion

The disparate case definitions for bovine abortion require standardisation. Bovine abortion rates are relatively higher than those of other farm animal species. ‘Normal’ abortion rates need to be determined for each geographic region, not extrapolated. Abortion diagnosis rates are increasing and more widespread application of molecular diagnostics will accelerate this trend.

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