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病毒性疾病对奶牛繁殖力的重要影响

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摘要

世界各地的牛群中有许多病毒性疾病是地方性疾病。许多病毒穿过胎盘并导致流产和胎儿畸形的能力是众所周知的。还有大量证据表明，病毒感染对于奶牛还有其他影响，反映在受胎率的降低上。但是，这些影响很大程度上取决于单个动物首次感染该疾病的时间，因此难以量化。本文介绍了5种可能影响奶牛繁殖力的病毒，以及它们的潜在作用机制。妊娠中期非细胞病变型牛病毒性腹泻病毒（bovine viral diarrhea virus, BVDV）的急性感染会使流产率升高或导致持续感染的犊牛出生。在临近配种期感染BVDV会直接影响卵巢和子宫内膜，导致发情周期不规律和早期胚胎死亡。BVDV诱发的免疫抑制也可能降低繁殖力，从而增加对细菌的易感性。牛疱疹病毒（bovine herpesvirus, BHV）-1型在青春期前的小母牛中最常见，会导致它们生长减缓，延迟繁殖并提高首次产犊的年龄，先前受感染的动物继而表现出繁殖力的降低。尽管这可能与肺损伤有关，但也有卵巢病变的相关报告。初次感染后，BHV-1和BHV-4都潜伏在宿主中，并且可能在以后由于应激而重新激活，如与产犊和早期泌乳有关的应激。虽然仅感染BHV-4可能不会降低繁殖力，但它似乎与已建立的细菌病原体（如大肠杆菌和化脓隐秘杆菌）共同作用，促进子宫内膜炎的发展并延迟产犊后母牛的子宫修复机制。施马伦贝格病毒（Schmallenberg virus, SBV）和蓝舌病病毒（bluetongue virus, BTV）均以昆虫作为媒介传播，导致流产率和先天畸形的增加。BTV-8同时还损害孵出囊泡的发育；此外，任何一种病毒在繁殖前后的感染基本都会降低受胎率。尽管受胎率的降低通常难以量化，但足以造成经济损失，这有助于衡量疫苗接种和根除方案的效益。

1. 引言

尽管病毒性疾病仍然是造成现代养牛业经济损失的主要原因，但人们通常低估了它对繁殖力的潜在影响，其主要作用机制也不甚清楚。贸易全球化、畜群规模扩大和环境变化等因素促使现有病原体扩散，并将疾病引入以前没有疾病的地区和动物种群[1]。低繁殖力和乳房健康/牛奶质量仍然是奶制品生产者关注的两大问题[2]。在繁殖方面，病毒导致的流产和胎儿畸形受到了最多关注[3]，感染结果通常取决于妊娠阶段的初始感染。然而，病毒性疾病对繁殖性能的影响更为普遍，通过降低受孕率和增加因未能及时受孕而被淘汰的风险，可以产生许多微妙的影响。除受精失败外，大约40%的牛早期胚胎在着床或受精后的前三周死亡，而母牛在21~24 d后又回到发情期。在妊娠的第24~60 d内又有10%~20%的胚胎死亡[4]。相比之下，牛场母牛的流产率通常很低（5%~10%），而且有许多通常难以确诊的潜在病因[5]。除了胎儿的死亡

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外，流产还会对母牛产生不利影响。根据妊娠期的不同，母牛可能需要重新配种（从而增加了产犊间隔），也可能过早地开始下一次泌乳。例如，在一项研究中，7768个荷斯坦小母牛的流产率为4.8%。这使它们在没有完成第一次泌乳的情况下离群的风险增加了2.73倍。未完成第一次泌乳的动物有1/3要么死亡，要么必须在产犊后50 d内被宰杀[6]。本文大致介绍5种通过不同机制影响奶牛繁殖力的病毒性感染。

2. 牛病毒性腹泻病毒

关于牛病毒性腹泻病毒（bovine viral diarrhea virus, BVDV）对繁殖力的影响已经展开了极为广泛的研究，人们对其内在致病机制了解得较多，因此首先对其进行最详细的讨论。BVDV是一种黄病毒科瘟病毒属的病毒，在世界上许多国家肆虐，个体和牛群中的流行率分别为40%~90%和28%~66%[7,8]。它的基因组是一条正义单链RNA，按基因组序列的差异可分为1型或2型（BVDV-1或BVDV-2）。还有第三种类型：BVDV-3（一种Hobi样非典型瘟病毒）。该病毒以非细胞致病型（non-cytopathogenic, ncp）或细胞致病型（cytopathogenic, cp）生物型存在，其中，ncp生物型会引起大部分临床损失[9]。BVDV表现出由母体至胎儿的垂直传播，具有广泛的组织嗜性，可以短暂或持续感染宿主[10]。此类RNA病毒表现出显著的遗传变异性，促进了新物种的出现[11]。哺乳动物细胞通常会对病毒感染应答而产生I型干扰素（type I interferon, IFN），然后触发一系列抗病毒途径。BVDV可通过抑制IFN的产生而引起免疫抑制，从而延迟了宿主的反应并增强了病毒完成其复制周期的能力[12,13]。

BVDV通常通过口鼻途径感染，但也可以通过精液或胚胎移植直接传播至生殖道[14,15]。急性感染的动物通常会在10~14 d内消除病毒，但在某些明显康复的动物中，具有传播能力的病毒可以持续更长时间[16]。在极少数情况下，公牛会持续感染睾丸（一个具有免疫特权的部位）。通常情况下，在初次急性感染后的几个月中，可以通过逆转录聚合酶链反应（reverse transcription polymerase chain reaction, RT-PCR）在精液中检测到BVDV，尽管在9周后似乎不太存在病毒传播的风险[15]。在免疫能力发育之前（即在妊娠第120天之前）感染ncp BVDV的胎儿会导致早期胚胎死亡、流产或持续感染（persistently infected, PI）的免疫耐受小牛出生[17]。PI小牛可以不断从所有分泌物中散播病毒，因此是牛群内的主要感染源。

急性BVD感染的影响在很大程度上取决于病毒的生物型和致病力，这可能导致抑制或启动凋亡和先天性免疫反应。ncp BVDV可通过多种方式抑制先天免疫反应[13,18]。该病毒首先被位于细胞内区室的toll样受体（TLR-3或TLR-7/TLR-8）或胞质模式识别受体（RIG-I, DDX58）检测单链RNA。TLR-3的下游信号通路包括IFN调节因子IRF-3和IRF-7，它们通常上调I型IFN的转录。BVDV蛋白质N^{pro}将IRF-3靶向蛋白酶体降解，从而抑制下游信号传导并防止IFN升高[18]。鸟苷酸结合蛋白4（guanylate-binding protein 4, GBP4）是一种可诱导IFN的GTP酶，也可以抑制该途径，同时保持NF-κB信号的完整性[19]。此外，分泌的BVDV结构蛋白E^{rns}可通过它的胞外功能，即作为核糖核酸酶降解病毒的RNA [20]。

BVDV造成的许多经济损失，除了在妊娠后期导致流产和胎儿畸形外，还包括低下的繁殖力[10,17]。BVDV诱导的免疫抑制作用增强了对其他疾病的敏感性，这也可能影响繁殖力。在受精前9天或受精后4天感染BVDV的实验中，奶牛受胎率下降了44%[21]。Fray等[22]的评述引用了在野外感染ncp BVDV的许多相似报道，尽管偶尔有相反的报道。从那时起，Rüfenacht等[23]使用个体的血清转化率来评估可能接触的时间，在瑞士奶牛场中以较高的BVDV流行率测量繁殖力参数。妊娠的前45 d感染对不返情率没有影响，但妊娠中期的感染会导致流产率从6.1%提高到15.8%。接触时间显得尤其关键，正如Rodning等[24]所述，当小母牛在开始繁殖前50 d被引入PI动物时，它们会产生主动免疫力，并且对繁殖能力没有不利影响。Newcomer等[25]对46个研究进行了综合分析，以确定针对BVDV的疫苗接种对三个妊娠结局的潜在益处。与未接种疫苗的牛群相比，接种疫苗的奶牛流产率和胎儿感染率分别降低了近45%和85%，而怀孕的风险虽然较小，但仍提高了约5%。由于缺乏大规模的统计学研究，这种幅度的变化在较小的研究中可能无法达到显著性。

已经提出了多种机制来解释因卵巢、子宫和早期胚胎的影响而导致的繁殖力降低。急性感染后60 d [26]，PI母牛的卵母细胞、卵泡细胞中可检测到BVDV抗原[27]。感染BVDV的动物会发展为卵泡炎[26]，并会影响排卵和卵巢类固醇生成[27–29]。当母牛被ncp型BVDV急性感染时，卵泡的生长方式会受到随后两个发

情周期的影响，使优势卵泡的生长减少[30]。同样，当母牛在同期发情之前9 d被感染时，黄体生成素（luteinizing hormone, LH）的波动性降低，从排卵到孕酮升高会有延迟，随后的孕酮水平也降低[28,31]。这些结果与研究结果相吻合，表明各种类型的压力对排卵机制有延迟或抑制作用[32,33]，而热应激和乳腺感染均可减少卵泡类固醇生成，破坏卵泡优势并减少排卵前LH激增[34]。在发情期这个关键阶段发生的任何急性感染都可能造成类似的影响。

子宫内膜也被认为是BVDV感染的主要部位[17,29]。通过尾静脉接种或通过与PI公牛交配将小母牛感染BVDV后7~16 d，在其子宫中发现了BVDV [14,35]，而初次感染24 d后从宫颈黏液中分离出ncp BVDV [22]。在一次屠宰场调查中，65头母牛中有23%的子宫内膜巨噬细胞样细胞中也检测到BVDV抗原[36]。有充分的证据表明，存在BVDV的子宫会通过两种机制对繁殖力产生有害影响：其一，诱发母牛病因向子宫内膜炎发展；其二，阻止母牛完成受孕。90%以上的母牛在产犊后，子宫内定植了许多细菌[37]。这些细菌应被黏膜免疫系统和固有的免疫反应迅速清除，这些免疫反应除了专有免疫细胞外，还包括子宫内膜上皮和基质细胞[38,39]。这种早期的先天反应对于避免子宫疾病的发展至关重要。然而，许多奶牛仍旧患有子宫炎或子宫内膜炎（估计分别占所有动物的40%和20%）[38]。在培养的牛子宫内膜细胞中，ncp型BVDV的感染抑制了多种免疫途径，这些免疫反应通常是在细菌脂多糖（lipopolysaccharide, LPS）的攻击下激活，包括下调许多干扰素刺激基因（interferon-stimulated gene, ISG），这是子宫防御机制的重要环节[40,41]。ncp BVDV感染还能够将子宫内膜产生的前列腺素（prostaglandin, PG）$F_{2\alpha}$转化为PGE_2[42]。人们认为$PGF_{2\alpha}$是一种免疫增强剂，而PGE_2则是一种免疫抑制剂，有促黄体的作用[43,44]。因此，这种转换也可能会降低子宫内膜对细菌的免疫反应，而且会增加母牛产生持续性卵巢黄体的可能性[45]，这种情况通常与子宫疾病有关[46]。

孕体分化的滋养外胚层可以产生干扰素tau蛋白（interferon tau, IFNT），用以实现母牛的母体妊娠识别[47,48]，从而抑制子宫内膜催产素受体的产生，防止黄体溶解[49,50]。IFNT是一种I型干扰素，与干扰素α（IFN-α）和干扰素β（IFN-β）有相似的结构，但在其启动中缺乏病毒反应元件，因此不会被病毒感染导致上调[51]。然而，IFNT却可以与子宫内膜上的相同IFN-α/IFNA-β受体结合。IFNT与孕酮一起作用于子宫内膜，以形成一个可以接受植入物的环境，包括多种ISG的正向调节[50,52,53]。子宫免疫的调节、间质重塑、子宫内膜腺体增生和子宫脉管系统的发育在母牛受孕中起决定性作用[52,54]。在体外，单一ncp型BVDV急性感染对子宫内膜基因的表达有一定的影响[40]。但是，感染确实干扰了由ISG调节的IRF-STAT1和STAT2抑制IFNT诱导的ISG表达的途径，包括*ISG15*、*HERC5*、*USP18*（有类泛素化修饰参与的蛋白质修饰），*DDX58*、*IFIH1*（病毒RNA的胞浆检测）及*IFIT3*、*MX2*、*RSAD2*和*SAMD9*（具有抗病毒活性的免疫调节剂）[41]。子宫内膜类泛素化修饰途径的上调是早期妊娠的一个重要环节，贯穿于整个哺乳动物的妊娠过程中[55]。因此，BVDV引起的抗病毒干扰素应答失调无疑会干扰子宫内膜中的IFNT信号传导，因此可能存在另一种机制，即在妊娠早期BVDV的感染使受胎率降低。

人们担心小母牛可能会在胚胎移植后产生BVDV，因此便针对BVDV对牛胚胎的影响进行了大量研究。由体内和体外技术产生的胚胎在从卵母细胞到孵化囊胚的所有阶段均已被ncp或cp病毒感染。BVDV对体内移植胚胎的亲和性随BVDV菌株的不同而变化[56,57]。在同期发情的第7天，在用于胚胎移植的培养基中接种1型ncp BVDV子宫，导致10头小母牛中有6头在30 d后怀孕，但是这些母体中的胎儿在接下来的30 d即死亡[58]。尽管BVDV在牛卵母细胞周围的卵丘细胞中有效复制，但这并不影响随后通过体外受精产生的囊胚发育[59]。同样，当卵母细胞、受精卵、8细胞胚胎、桑椹胚和孵化囊胚感染了ncp或cp病毒，同时透明带还未成型时，cp BVDV仅对发育产生不利影响[60]。在最近的一项研究中，将卵母细胞复合体用不同剂量的BVDV-1、BVDV-2或BVDV-3感染[57]。BVDV-1对已经发育的胚胎并无影响，而BVDV-2感染增加了卵裂率，但不影响囊胚发育率。在这两种情况下，退化的胚胎均检测为阳性。总之，感染BVDV-1和BVDV-2的卵母细胞可以正常发育，但携带病毒。BVDV-3（Hobi样病毒）降低了卵裂率和囊胚发育率，因此可能导致胚胎移植入体内前即死亡。Bielanski等[35]在超排母牛体内移入了来自PI公牛的精液，收集了第7天的胚胎，并将清洗过的胚胎转移到未感染的母牛身上。尽管在移植前的胚胎中检测到了BVDV，但它并未感染新宿主。由此项实验可得出，如果按照国际胚胎移植学会的建议[61]，采用了正确的洗涤程序，那么BVDV通过胚胎移植传播到宿主母牛的

风险很小。这也通过灵敏的定量聚合酶链反应（quantitative polymerase chain reaction, qPCR）技术证实了检测的病毒拷贝数较低[62]。

总而言之，ncp BVDV急性感染通过调节免疫途径的综合作用，使卵巢和子宫内膜组织发生细胞内变化。这会影响发情周期不规则、早期胚胎死亡和免疫抑制，从而降低母牛的繁殖能力。妊娠中期感染则会使流产率提高或导致PI犊牛出生。

3. 牛疱疹病毒 1 型

牛传染性鼻气管炎（infectious bovine rhinotracheitis, IBR）是一种由牛疱疹病毒1型（bovine herpesvirus-1, BHV-1）引起的高度传染性呼吸系统疾病，其特征是上呼吸道发生急性炎症。BHV-1是疱疹病毒科α-疱疹病毒亚科病毒。虽然一些国家已经消灭了IBR [63]，但在英国和爱尔兰等许多地方，该病仍是奶牛的地方病[8,64]。最近的一项荟萃分析发现，中国的牛中，BHV-1的总患病率为40% [65]。BHV-1是造成犊牛肺炎的主要因素，而犊牛肺炎仍然是1~5个月龄奶牛死亡和发病的最常见原因[66]。BHV-1还可引起结膜炎、流产、脑炎和全身感染[5,63]。首次感染后，该病毒不能被完全消灭，而是潜伏在大脑的神经细胞中。在应激状态下，它可以通过糖皮质激素的增加而被重新激活[67–69]。BHV-1是导致牛呼吸道疾病（bovine respiratory disease, BRD）的多种病原体之一，还包括其他几种病毒[即牛呼吸道合胞病毒（bovine respiratory syncytial virus, BRSV）、副流感病毒3型（parainfluenza III virus, PI3）、BVDV和冠状病毒]、细菌（如溶血性曼氏杆菌、嗜血杆菌、巴氏杆菌和支原体）和真菌（如曲霉菌）[70]。

世界各国进行了大量的流行病学研究，研究表明高达46%的犊牛患有BRD [70,71]。对于存活下来的犊牛，越来越多的证据表明，在幼年时期患有的疾病对成年表现有长期影响[72,73]。受BRD影响的动物生长速度降低[71,74]，因此，首次繁殖和首次产犊的年龄也延迟了。这通常与支气管肺损伤和胸膜粘连有关[75]。例如，在出生后三个月内患有BRD的母牛中，首次分娩推迟时间的中位数是6个月[76]。Bach [74]报道说，与健康小牛相比，首次产犊前发生4次BRD的小牛，首次泌乳失败的概率要高（1.87±0.14）倍。另一项研究发现，出生后三个月内经历严重BRD的母牛，成熟后产犊间隔增加了12%[77,78]。在某季节性产犊的爱尔兰牛群中，与大缸奶经BHV-1酶联免疫吸附试验（ELISA）确认为阴性的牛群相比，BHV-1阳性的牛群的经产奶牛三周产犊率明显较低[79]。埃塞俄比亚两项相关的流行病学研究发现，对BHV-1血清反应呈阳性的母牛，子宫感染率和胎膜残留率明显更高[80,81]。对7500多只动物进行的荟萃分析显示，接种BHV-1疫苗后，怀孕母牛的流产风险总体降低了60% [82]。

许多研究调查了在配种期间用改良的IBR活疫苗治疗牛的效果。发情期接种[83]、发情期后第1天接种[84]、配种后第7天或第14天接种[85]的小母牛出现轻度的卵巢炎，其特征是黄体中有坏死灶、少量坏死卵泡和单核细胞集聚。在配种后第21天或第28天后接种的小母牛，黄体没有病变，但有大量坏死的卵泡[85]。在未分离出BHV-1的卵巢中未发现此类病变[84]。在发情期接种疫苗后，循环黄体酮减少[84,86]；受孕率也降低[86,87]。虽然这一综述主要涉及奶牛，但有证据表明，6个月大时感染BHV-1的青年公牛在6个月后精子质量下降[88]。Givens [89]最近回顾了一些病毒性疾病对公牛的影响以及这些疾病通过精液传播的风险。

综上所述，犊牛发生BRD的比例高，常与BHV-1感染相关。这减慢了生长，导致初产年龄增加。繁殖力、被扑杀的风险和流产率都随之增加。关于感染对生殖道的直接影响的资料很少，但有一些证据表明感染对卵巢功能有直接影响。

4. 牛疱疹病毒 4 型

牛疱疹病毒4型（BHV-4）是一种双链DNA病毒，在某些奶牛群中高度流行，与繁殖力降低有关[90,91]。与其他疱疹病毒一样，感染某些类型的细胞（包括巨噬细胞）后，该病毒可以潜伏在宿主体内。这导致了持续感染[92]，可以通过糖皮质激素在体外重新激活[93,94]。通过血清型的检测，有证据表明该病毒也可以在围产期的体内重新激活[95]，并与临床子宫炎[96]相关。

与BVDV相同的是，BHV-4可以轻易感染子宫，被认定为与子宫炎和子宫内膜炎相关。但是，该病毒对于繁殖力的影响还不清楚，因为它经常出现在未发生子宫感染的对照牛体内。此外，被检测的母牛通常也对已知细菌病原体呈阳性，包括大肠杆菌、化脓隐秘杆菌、链球菌和索氏嗜血杆菌[97–100]。但是，有证据表明BHV-4可能与繁殖力下降有关。将需要一次或两次授精才能受孕的奶牛同需要两次以上授精的奶牛进行比较，

发现需要更多授精的奶牛BHV-4的发生率更高[101]。Klamminger等[100]也记录了受感染动物在产犊后80 d内授精或200 d内受孕的风险降低。

与ncp BVDV不同的是，BHV-4具有细胞病变作用，感染后可以杀死子宫内膜上皮和基质细胞[102,103]。越来越多的证据表明，BHV-4可以与某些已确定的子宫病原体共同促进子宫内膜炎发展[99,104,105]。BHV-4的复制取决于立即早期基因2（immediate early gene 2, IE2）的反式激活，该启动子可以被PGE_2、肿瘤坏死因子-α（TNF-α）、大肠杆菌和LPS上调，这些物质均与子宫内膜的细菌感染有关[104,106]。相反，BHV-4可以激活子宫内膜细胞中的白介素（interleukin, IL）-8基因启动子[103,107]。这是将粒细胞吸引到子宫的关键趋化因子。在最近的一项研究中，Tebaldi等[108]在培养的牛子宫内膜基质细胞上测量了BHV-4感染引起的全局基因转录。除IL-8外，另一个主要的激活途径是基质金属蛋白酶（matrix metalloproteinase, MMP）-1的上调。MMP参与产后子宫内膜的重塑[109]，对于控制免疫调节方面也很重要。一方面，它们的蛋白水解活性可以促进免疫细胞迁移并激活细胞因子，如IL-1、IL-8、TNF-α和防御素[110]。另一方面，MMP的过度活化与许多免疫病理结果相关（参见文献[108]）。

总之，迄今为止的证据表明，BHV-4感染在奶牛中非常普遍。该病毒本身可能不会引起临床子宫疾病，但是在奶牛产犊后，该病毒在子宫内膜中可以从潜伏状态被重新激活，然后与细菌性病原体共同作用，通过破坏先天免疫力并削弱子宫修复机制，增加患子宫疾病的风险。

5. 施马伦贝格病毒

施马伦贝格病毒（Schmallenberg virus, SBV）最早于2011年在欧洲出现。系统发育分析表明，它属于正布尼亚病毒属（*Orthobunyavirus*）的Simbu血清群[111]。SBV由库蠓属（*Culicoides*）昆虫传播，会影响家养和野生反刍动物，包括绵羊、山羊和牛。成年母牛感染后的临床症状相当轻微，包括发烧、产奶量下降、感染后4~7 d出现腹泻，并且病毒血症达到高峰[112]。SBV可以在胎盘中持续存在，也可以穿过胎盘在胎儿体内进行复制[113]。根据暴露时间的不同，这可能会导致流产或严重的先天畸形，从而导致难产和死胎的出生[114,115]。一项针对瑞士奶牛场的病例对照研究发现，2012年SBV感染开始后，流产率上升至6.5%，而上一年的流产率则为3.7%[116]。

虽然这些对胎儿的影响是该病最明显的症状，但也有证据表明该病对受孕和（或）早期胚胎发育有不利影响。与BVDV类似，怀孕初期感染SBV可能会干扰IFNT的产生，从而危害孕体的存活。与BVDV一样，SBV使用一种非结构蛋白来降解细胞RNA聚合酶II，从而抑制I型IFN产生，并增强毒性[117]。Veldhuis等[118]在一项研究中从牛群水平评估了2011年该流行病对荷兰和德国部分地区奶牛生产力的影响，该研究将疾病流行期间的牛奶产量、繁殖力和死亡率与较早时期的数据进行比较。在这两个国家中，该病流行期间的繁殖参数都有小幅但显而易见的下降，包括所需重复授精次数显著增加，56 d不返情率下降了约5%（从61.5%降至55.7%）。基于SBV对瑞士奶牛的影响，进行了进一步分析[119]。该分析对个体动物层面进行，并类似地发现，疾病流行期间，与来自病例组和对照组的非临床动物相比，具有症状母牛的人工授精次数更高。在这项研究中，不返情率没有受到影响，尽管这可能是由于农场的干预，即停止了对感染的动物在感染期间的授精。

6. 蓝舌病病毒

蓝舌病病毒（BTV）是一种重要的环状病毒属病毒，可能感染家养和野生反刍动物。该病毒的地理分布主要取决于昆虫媒介库蠓属昆虫[120]。BTV存在许多血清型，包括目前在欧洲使用的BTV-8菌株[121]。除了可能导致高发病率和高死亡率并降低产奶量外，BTV还会影响奶牛的繁殖力[122,123]。该病毒可以穿过胎盘，在妊娠130 d之前被感染的牛胎会形成致命的中枢神经系统畸形[124]。后来对BTV-8的研究也发现新生犊牛先天畸形的发生率更高[122]。在加利福尼亚的一项研究中，BTV血清学阳性的母牛首次产犊的年龄明显更大[125]。2007年比利时暴发BTV-8期间，牛胎死亡率增大了[126]。一项早期的流行病学研究证实牛的受胎率降低，产犊间隔时间延长[124]。最近，荷兰BTV-8暴发后获得的数据证实了这一点[127]。这项研究发现，受感染的母牛在第一次人工授精（artificial insemination, AI）后56 d内复配的可能性是普通母牛的5倍，而所需人工授精的次数则是1.7倍。Nusinovici等[123]使用了另一种分析方法，其提供的证据表明，如果感染BTV-8的法国奶牛在疾病发现日前四周到后五周期间内接受授精，

那么其受精能力下降。总之，这些研究提供了良好的证据，表明BTV-8感染会阻止初始受孕和（或）对早期胚胎产生不利影响。

在着床前的实验性感染中，只有具有透明带的牛胚胎具有细胞病变性。没有证据表明在患有病毒血症的母体中，BTV传播到了早期胚胎[128]。然而，第8~9天孵化的囊胚易受BTV-8感染表现出生长停滞和凋亡增加[129]。证据再次表明BTV具有抑制IFN合成的能力。在这种情况下，病毒NS4蛋白能够通过下调1型干扰素和ISG的表达来抵消宿主的免疫反应[130]。如上文对BVDV的讨论所述，这可能会消除与母体妊娠识别相关的信号。

7. 结论和展望

本文的文献综述证实，许多常见的牛病毒感染对奶牛的繁殖力有不利影响。人工流产和胎儿异常很容易量化，尽管在许多情况下致病因素仍然未知。相反，难以可靠地检测受胎率的降低。疾病的影响取决于动物被感染时生殖周期的确切阶段，并受畜群和季节的影响。一些病毒可能会保持潜伏状态，产犊前后的重新激活很可能与泌乳早期的代谢应激有关。其他病毒通过直接或间接地促进宿主的免疫抑制，与其他传染源产生协同作用。这可能会中断繁殖过程，如排卵和着床，同时使动物容易被生殖道细菌感染。在这一领域，决定对繁殖力的显著影响取决于在研究中是否有显著的力量来发现潜在的小变化。我们无法获得影响繁殖力的许多其他因素的可靠数据，如疾病史、疫苗接种史，以及母牛个体当前的代谢状况，这也使情况变得复杂。主要使用子宫内膜细胞和胚胎的体外研究为作用机制提供了有用的证据。然而，很少对病毒在体内感染对生殖道的影响进行全面的研究。考虑到所涉及的成本和在足够长的时间内将感染奶牛维持在隔离设施中的实际情况，这是可以理解的。尽管存在这些局限性，但现有数据确实表明，病毒性疾病在降低奶牛的繁殖力中起着关键的作用，但目前尚未得到充分研究。

考虑到病毒性疾病在全球牛生产中的重要性，消除或至少减少此类疾病的流行至关重要。严格的检疫程序可以有助于防止新型疾病在国家之间传播。国家政策可以激励农民增加常规检测和疫苗接种的频率。地方监管组织必须保持警惕，在新发病毒性疾病或现有病毒的变异株出现后尽快进行检测。新技术也可以促进疾病监测，如基于全血RNA测序数据的生物信息学分析的病原体发现计算方法[131]。此类措施应该通过提高牛群的受胎率和使用年限来获得回报。

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Compliance with ethics guidelines

D. Claire Wathes, Chike F. Oguejiofor, Carole Thomas, and Zhangrui Cheng declare that they have no conflict of interest or financial conflicts to disclose.

References

[1] Newcomer BW, Walz PH, Givens MD. Potential applications for antiviral therapy and prophylaxis in bovine medicine. Anim Health Res Rev 2014;15(1):102–17.
[2] More SJ, McKenzie K, O'Flaherty J, Doherty ML, Cromie AR, Magan MJ. Setting priorities for non-regulatory animal health in Ireland: results from an expert Policy Delphi study and a farmer priority identification survey. Prev Vet Med 2010;95(3–4):198–207.
[3] Ali H, Ali AA, Atta MS, Cepica A. Common, emerging, vector-borne and infrequent abortogenic virus infections of cattle. Transbound Emerg Dis 2012;59(1):11–25.
[4] Wathes DC, Diskin MG. Reproduction, events and management: Mating management: fertility. In: Reference module in food sciences. Amsterdam: Elsevier; 2015. p. 1–11.
[5] Daniel Givens M, Marley MSD. Infectious causes of embryonic and fetal mortality. Theriogenology 2008;70(3):270–85.
[6] Bach A. Ruminant nutrition symposium: optimizing performance of the Offspring: nourishing and managing the dam and postnatal calf for optimal lactation, reproduction, and immunity. J Anim Sci 2012;90(6):1835–45.
[7] Walz PH, Grooms DL, Passler T, Ridpath JF, Tremblay R, Step DL, et al. Control of bovine viral diarrhea virus in ruminants. J Vet Intern Med 2010;24(3):476–86.
[8] Velasova M, Damaso A, Prakashbabu BC, Gibbons J, Wheelhouse N, Longbottom D, et al. Herd-level prevalence of selected endemic infectious diseases of dairy cows in Great Britain. J Dairy Sci 2017;100(11):9215–33.
[9] Ridpath JF. BVDV genotypes and biotypes: practical implications for diagnosis and control. Biologicals 2003;31(2):127–31.
[10] Peterhans E, Schweizer M. Pestiviruses: how to outmaneuver your hosts. Vet Microbiol 2010;142(1–2):18–25.
[11] Eigen M. Viral quasispecies. Sci Am 1993;269(1):42–9.
[12] Charleston B, Carr BV, Morrison WI, Fray MD, Baigent S. Establishment of persistent infection with non-cytopathic bovine viral diarrhoea virus in cattle is associated with a failure to induce type I interferon. J Gen Virol 2001;82(Pt 8):1893–7.
[13] Baigent SJ, Goodbourn S, McCauley JW. Differential activation of interferon regulatory factors-3 and -7 by non-cytopathogenic and cytopathogenic bovine viral diarrhoea virus. Vet Immunol Immunopathol 2004;100(3–4):135–44.
[14] Bielanski A, Sapp T, Lutze-Wallace C. Association of bovine embryos produced by in vitro fertilization with a noncytopathic strain of bovine viral diarrhea virus type II. Theriogenology 1998;49(6):1231–8.

[15] Givens MD, Riddell KP, Edmondson MA, Walz PH, Gard JA, Zhang Y, et al. Epidemiology of prolonged testicular infections with bovine viral diarrhea virus. Vet Microbiol 2009;139(1–2):42–51.

[16] Collins ME, Heaney J, Thomas CJ, Brownlie J. Infectivity of pestivirus following persistence of acute infection. Vet Microbiol 2009;138(3–4):289–96.

[17] Lanyon SR, Hill FI, Reichel MP, Brownlie J. Bovine viral diarrhoea: pathogenesis and diagnosis. Vet J 2014;199(2):201–9.

[18] Chen Z, Rijnbrand R, Jangra RK, Devaraj SG, Qu L, Ma Y, et al. Ubiquitination and proteasomal degradation of interferon regulatory factor-3 induced by Npro from a cytopathic bovine viral diarrhea virus. Virology 2007;366(2):277–92.

[19] Wang J, Liu B, Wang N, Lee YM, Liu C, Li K. TRIM56 is a virus- and interferoninducible E3 ubiquitin ligase that restricts pestivirus infection. J Virol 2011;85(8):3733–45.

[20] Zürcher C, Sauter KS, Schweizer M. Pestiviral Erns blocks TLR-3-dependent IFN synthesis by LL37 complexed RNA. Vet Microbiol 2014;174(3–4):399–408.

[21] McGowanMR, Kirkland PD, Rodwell BJ,KerrDR, Carroll CL.A fieldinvestigation of the effects ofbovine viral diarrhea virus infection around the time of insemination on the reproductive performance of cattle. Theriogenology 1993;39(2):443–9.

[22] Fray MD, Paton DJ, Alenius S. The effects of bovine viral diarrhoea virus on cattle reproduction in relation to disease control. Anim Reprod Sci 2000;60–61:615–27.

[23] Rüfenacht J, Schaller P, Audigé L, Knutti B, Küpfer U, Peterhans E. The effect of infection with bovine viral diarrhea virus on the fertility of Swiss dairy cattle. Theriogenology 2001;56(2):199–210.

[24] Rodning SP, Givens MD, Marley MS, Zhang Y, Riddell KP, Galik PK, et al. Reproductive and economic impact following controlled introduction of cattle persistently infected with bovine viral diarrhea virus into a naive group of heifers. Theriogenology 2012;78(7):1508–16.

[25] Newcomer BW, Walz PH, Givens MD, Wilson AE. Efficacy of bovine viral diarrhea virus vaccination to prevent reproductive disease: a meta-analysis. Theriogenology 2015;83(3):360–5.

[26] Grooms DL, Brock KV, Pate JL, Day ML. Changes in ovarian follicles following acute infection with bovine viral diarrhea virus. Theriogenology 1998;49 (3):595–605.

[27] Fray MD, Mann GE, Clarke MC, Charleston B. Bovine viral diarrhoea virus: its effects on ovarian function in the cow. Vet Microbiol 2000;77(1–2):185–94.

[28] Kafi M, McGowan MR, Kirkland PD, Jillella D. The effect of bovine pestivirus infection on the superovulatory response of Friesian heifers. Theriogenology 1997;48(6):985–96.

[29] Grooms DL. Reproductive consequences of infection with bovine viral diarrhea virus. Vet Clin North Am Food Anim Pract 2004;20(1):5–19.

[30] Grooms DL, Brock KV, Ward LA. Detection of bovine viral diarrhea virus in the ovaries of cattle acutely infected with bovine viral diarrhea virus. J Vet Diagn Invest 1998;10(2):125–9.

[31] Fray MD, Mann GE, Bleach EC, Knight PG, Clarke MC, Charleston B. Modulation of sex hormone secretion in cows by acute infection with bovine viral diarrhoea virus. Reproduction 2002;123(2):281–9.

[32] Dobson H, Smith RF. What is stress, and how does it affect reproduction? Anim Reprod Sci 2000;60–61:743–52.

[33] Dobson H, Walker SL, Morris MJ, Routly JE, Smith RF. Why is it getting more difficult to successfully artificially inseminate dairy cows? Animal 2008;2 (8):1104–11.

[34] Roth Z, Wolfenson D. Comparing the effects of heat stress and mastitis on ovarian function in lactating cows: basic and applied aspects. Domest Anim Endocrinol 2016;56(Suppl):S218–27.

[35] Bielanski A, Algire J, Lalonde A, Garceac A. Embryos produced from fertilization with bovine viral diarrhea virus (BVDV)-infected semen and the risk of disease transmission to embryo transfer (ET) recipients and offspring. Theriogenology 2013;80(5):451–5.

[36] Firat I, Ak S, Bozkurt HH, Ak K, Turan N, Bagcigil F. Distribution of bovine viral diarrhea virus (BVDV) in the genital system tissues of cattle. Vet Arh 2002;72:235–48.

[37] Sheldon IM, Lewis GS, LeBlanc S, Gilbert RO. Defining postpartum uterine disease in cattle. Theriogenology 2006;65(8):1516–30.

[38] Sheldon IM, Cronin J, Goetze L, Donofrio G, Schuberth HJ. Defining postpartum uterine disease and the mechanisms of infection and immunity in the female reproductive tract in cattle. Biol Reprod 2009;81 (6):1025–32.

[39] Oguejiofor CF, Cheng Z, Abudureyimu A, Fouladi-Nashta AA, Wathes DC. Global transcriptomic profiling of bovine endometrial immune response in vitro. I. Effect of lipopolysaccharide on innate immunity. Biol Reprod 2015;93(4):100.

[40] Oguejiofor CF, Cheng Z, Abudureyimu A, Anstaett OL, Brownlie J, Fouladi-Nashta AA, et al. Global transcriptomic profiling of bovine endometrial immune response in vitro. II. Effect of bovine viral diarrhea virus on the endometrial response to lipopolysaccharide. Biol Reprod 2015;93(4):101.

[41] Cheng Z, Chauhan L, Barry AT, Abudureyimu A, Oguejiofor CF, Chen X, et al. Acute bovine viral diarrhea virus infection inhibits expression of interferon s-stimulated genes in bovine endometrium. Biol Reprod 2017;96 (6):1142–53.

[42] Cheng Z, Abudureyimu A, Oguejiofor CF, Ellis R, Barry AT, Chen X, et al. BVDV alters uterine prostaglandin production during pregnancy recognition in cows. Reproduction 2016;151(6):605–14.

[43] Lewis GS. Steroidal regulation of uterine resistance to bacterial infection in livestock. Reprod Biol Endocrinol 2003;1(1):117.

[44] Herath S, Lilly ST, Fischer DP, Williams EJ, Dobson H, Bryant CE, et al. Bacterial lipopolysaccharide induces an endocrine switch from prostaglandin F2a to prostaglandin E2 in bovine endometrium. Endocrinology 2009;150(4):1912–20.

[45] Arosh JA, Banu SK, Kimmins S, Chapdelaine P, Maclaren LA, Fortier MA. Effect of interferon-s on prostaglandin biosynthesis, transport, and signaling at the time of maternal recognition of pregnancy in cattle: evidence of polycrine actions of prostaglandin E2. Endocrinology 2004;145(11):5280–93.

[46] Opsomer G, Gröhn YT, Hertl J, Coryn M, Deluyker H, De Kruif A. Risk factors for post partum ovarian dysfunction in high producing dairy cows in Belgium: a field study. Theriogenology 2000;53(4):841–57.

[47] Kimura K, Spate LD, Green MP, Murphy CN, Seidel Jr GE, Roberts RM. Sexual dimorphism in interferon-tau production by in vivo-derived bovine embryos. Mol Reprod Dev 2004;67(2):193–9.

[48] Roberts RM. Interferon-s, a type 1 interferon involved in maternal recognition of pregnancy. Cytokine Growth Factor Rev 2007;18(5–6):403–8.

[49] Wathes DC, Lamming GE. The oxytocin receptor, luteolysis and the maintenance of pregnancy. J Reprod Fertil Suppl 1995;49:53–67.

[50] Lonergan P, Forde N. Maternal–embryo interaction leading up to the initiation of implantation of pregnancy in cattle. Animal 2014;8(Suppl 1):64–9.

[51] Roberts RM, Ealy AD, Alexenko AP, Han CS, Ezashi T. Trophoblast interferons. Placenta 1999;20(4):259–64.

[52] Bazer FW. Pregnancy recognition signaling mechanisms in ruminants and pigs. J Anim Sci Biotechnol 2013;4(1):23.

[53] Forde N, Carter F, Spencer TE, Bazer FW, Sandra O, Mansouri-Attia N, et al. Conceptus–induced changes in the endometrial transcriptome: how soon does the cow know she is pregnant? Biol Reprod 2011;85(1):144–56.

[54] Hansen PJ. The immunology of early pregnancy in farm animals. Reprod Domest Anim 2011;46(Suppl 3):18–30.

[55] Hansen TR, Pru JK. ISGylation: a conserved pathway in mammalian pregnancy. Adv Exp Med Biol 2014;759:13–31.

[56] Waldrop JG, Stringfellow DA, Riddell KP, Galik PK, Riddell MG, Givens MD, et al. Different strains of noncytopathic bovine viral diarrhea virus (BVDV) vary in their affinity for in vivo-derived bovine embryos. Theriogenology 2004;62(1–2):45–55.

[57] Da Silva Cardoso Pinto V, Alves MF, de Souza Nunes Martins M, Basso AC, Tannura JH, Pontes JHF, et al. Effects of oocytes exposure to bovine diarrhea viruses BVDV-1, BVDV-2 and Hobi-like virus on in vitro-produced bovine embryo development and viral infection. Theriogenology 2017; 97:67–72.

[58] Gard JA, Givens MD, Marley MS, Galik PK, Riddell KP, Edmondson MA, et al. Intrauterine inoculation of seronegative heifers with bovine viral diarrhea virus concurrent with transfer of in vivo-derived bovine embryos. Theriogenology 2010;73(8):1009–17.

[59] Tsuboi T, Imada T. Noncytopathogenic and cytopathogenic bovine viral diarrhea-mucosal disease viruses do not affect in vitro embryonic development into the blastocyst stage. Vet Microbiol 1996;49(1–2):127–34.

[60] Vanroose G, Nauwynck H, Soom AV, Vanopdenbosch E, Kruif A. Replication of cytopathic and noncytopathic bovine viral diarrhea virus in zona-free and zona-intact in vitro-produced bovine embryos and the effect on embryo quality. Biol Reprod 1998;58(3):857–66.

[61] Gard JA, Givens MD, Stringfellow DA. Bovine viral diarrhea virus (BVDV): epidemiologic concerns relative to semen and embryos. Theriogenology 2007;68(3):434–42.

[62] Gard JA, Givens MD, Marley MS, Galik PK, Riddell KP, Stringfellow DA, et al. Bovine viral diarrhea virus (BVDV) associated with single *in vivo*-derived and in vitro-produced preimplantation bovine embryos following artificial exposure. Theriogenology 2009;71(8):1238–44.

[63] Ackermann M, Engels M. Pro and contra IBR-eradication. Vet Microbiol 2006;113(3–4):293–302.

[64] Ring SC, Graham DA, Sayers RG, Byrne N, Kelleher MM, Doherty ML, et al. Genetic variability in the humoral immune response to bovine herpesvirus-1 infection in dairy cattle and genetic correlations with performance traits. J Dairy Sci 2018;101(7):6190–204.

[65] Chen X, Wang X, Qi Y, Wen X, Li C, Liu X, et al. Meta-analysis of prevalence of bovine herpes virus 1 in cattle in the mainland of China. Acta Trop 2018;187:37–43.

[66] McGuirk SM. Disease management of dairy calves and heifers. Vet Clin North Am Food Anim Pract 2008;24(1):139–53.

[67] Miller JM, Van der Maaten MJ. Effect of primary and recurrent infections bovine rhinotracheitis virus infection on the bovine ovary. Am J Vet Res 1985;46(7):1434–7.

[68] Rock D, Lokensgard J, Lewis T, Kutish G. Characterization of dexamethasoneinduced reactivation of latent bovine herpesvirus 1. J Virol 1992;66 (4):2484–90.

[69] Inman M, Lovato L, Doster A, Jones C. A mutation in the latency-related gene of bovine herpesvirus 1 disrupts the latency reactivation cycle in calves. J

Virol 2002;76(13):6771–9.
[70] Johnson KF, Burn CC, Wathes DC. Rates and risk factors for contagious disease and mortality in young dairy heifers. CAB Rev Perspect Agric Vet Sci Nutr Nat Resour 2011;6(059):1–10.
[71] Johnson KF, Chancellor N, Burn CC, Wathes DC. Analysis of pre-weaning feeding policies and other risk factors influencing growth rates in calves on 11 commercial dairy farms. Animal 2018;12(7):1413–23.
[72] Waltner-Toews D, Martin SW, Meek AH. The effect of early calfhood health status on survivorship and age at first calving. Can J Vet Res 1986;50 (3):314–7.
[73] Svensson C, Liberg P. The effect of group size on health and growth rate of Swedish dairy calves housed in pens with automatic milk-feeders. Prev Vet Med 2006;73(1):43–53.
[74] Bach A. Associations between several aspects of heifer development and dairy cow survivability to second lactation. J Dairy Sci 2011;94(2):1052–7.
[75] Thompson PN, Stone A, Schultheiss WA. Use of treatment records and lung lesion scoring to estimate the effect of respiratory disease on growth during early and late finishing periods in South African feedlot cattle. J Anim Sci 2006;84(2):488–98.
[76] Correa MT, Curtis CR, Erb HN, White ME. Effect of calfhood morbidity on age at first calving in New York Holstein herds. Prev Vet Med 1988;6(4):253–62.
[77] Hultgren J, Svensson C. Calving interval in dairy cows in relation to heifer rearing conditions in southwest Sweden. Reprod Domest Anim 2010;45 (1):136–41.
[78] Svensson C, Hultgren J. Associations between housing, management, and morbidity during rearing and subsequent first-lactation milk production of dairy cows in Southwest Sweden. J Dairy Sci 2008;91(4):1510–8.
[79] Sayers RG. Associations between exposure to bovine herpesvirus 1 (BoHV-1) and milk production, reproductive performance, and mortality in Irish dairy herds. J Dairy Sci 2017;100(2):1340–52.
[80] Asmare K, Sibhat B, Ayelet G, Gebremedhin EZ, Lidete KA, Skjerve E. Serological evidence of bovine herpesvirus-1, bovine viral diarrhea virus and Schmallenberg virus infections in relation to reproductive disorders in dairy cattle in Ethiopia. Acta Trop 2018;178:236–41.
[81] Sibhat B, Ayelet G, Skjerve E, Gebremedhin EZ, Asmare K. Bovine herpesvirus- 1 in three major milk sheds of Ethiopia: serostatus and association with reproductive disorders in dairy cattle. Prev Vet Med 2018;150:126–32.
[82] Newcomer BW, Cofield LG, Walz PH, Givens MD. Prevention of abortion in cattle following vaccination against bovine herpesvirus 1: a meta-analysis. Prev Vet Med 2017;138:1–8.
[83] Smith PC, Nusbaum KE, Kwapien RP, Stringfellow DA, Driggers K. Necrotic oophoritis in heifers vaccinated intravenously with infectious bovine rhinotracheitis virus vaccine during estrus. Am J Vet Res 1990;51 (7):969–72.
[84] Van der Maaten MJ, Miller JM, Whetstone CA. Ovarian lesions induced in heifers by intravenous inoculation with modified-live infectious bovine rhinotracheitis virus on the day after breeding. Am J Vet Res 1985;46 (9):1996–9.
[85] Miller JM, Van der Maaten MJ. Experimentally induced infectious bovine rhinotracheitis virus infection during early pregnancy: effect on the bovine corpus luteum and conceptus. Am J Vet Res 1986;47(2):223–8.
[86] Perry GA, Zimmerman AD, Daly RF, Buterbaugh RE, Rhoades J, Scholz D, et al. The effects of vaccination on serum hormone concentrations and conception rates in synchronized naive beef heifers. Theriogenology 2013;79(1):200–5.
[87] Chiang BC, Smith PC, Nusbaum KE, Stringfellow DA. The effect of infectious bovine rhinotracheitis vaccine on reproductive efficiency in cattle vaccinated during estrus. Theriogenology 1990;33(5):1113–20.
[88] Alm K, Koskinen E, Vahtiala S, Andersson M. Acute BRSV infection in young AI bulls: effect on sperm quality. Reprod Domest Anim 2009;44(3):456–9.
[89] Givens MD. Review: risks of disease transmission through semen in cattle. Animal 2018;12(Suppl 1):S165–71.
[90] Donofrio G, Franceschi V, Capocefalo A, Cavirani S, Sheldon IM. Isolation and characterization of bovine herpesvirus 4 (BoHV-4) from a cow affected by post partum metritis and cloning of the genome as a bacterial artificial chromosome. Reprod Biol Endocrinol 2009;7(1):83.
[91] Chastant-Maillard S. Impact of bovine herpesvirus 4 (BoHV-4) on reproduction. Transbound Emerg Dis 2015;62(3):245–51.
[92] Osorio FA, Reed DE. Experimental inoculation of cattle with bovine herpesvirus-4: evidence for a lymphoid-associated persistent infection. Am J Vet Res 1983;44(6):975–80.
[93] Dubuisson J, Thiry E, Bublot M, Thomas I, Van Bressem MF, Coignoul F, et al. Experimental infection of bulls with a genital isolate of bovine herpesvirus-4 and reactivation of latent virus with dexamethasone. Vet Microbiol 1989;21 (2):97–114.
[94] Donofrio G, van Santen VL. A bovine macrophage cell line supports bovine herpesvirus-4 persistent infection. J Gen Virol 2001;82(Pt 5):1181–5.
[95] Graham DA, McNeill GJ, Calvert V, Mawhinney K, Curran W, Ball NW, et al. Virological and serological evidence of bovine herpesvirus type 4 in cattle in Northern Ireland. Vet Rec 2005;157(18):539–43.
[96] Nikolin VM, Donofrio G, Milosevic B, Taddei S, Radosavljevic V, Milicevic V. First Serbian isolates of bovine herpesvirus 4 (BoHV-4) from a herd with a history of postpartum metritis. New Microbiol 2007;30(1):53–7.
[97] Frazier K, Pence M, Mauel MJ, Liggett A, Hines ME II, Sangster L, et al. Endometritis in postparturient cattle associated with bovine herpesvirus-4 infection: 15 cases. J Vet Diagn Invest 2001;13(6):502–8.
[98] Monge A, Elvira L, Gonzalez JV, Astiz S, Wellenberg GJ. Bovine herpesvirus 4-associated postpartum metritis in a Spanish dairy herd. Res Vet Sci 2006;80 (1):120–5.
[99] Szenci O, Sassi G, Fodor L, Molnár L, Szelényi Z, Tibold J, et al. Co-infection with bovine herpesvirus 4 and *Histophilus somni* significantly extends the service period in dairy cattle with purulent vaginal discharge. Reprod Domest Anim 2016;51(1):143–9.
[100] Klamminger S, Prunner I, Giuliodori MJ, Drillich M. Uterine infection with bovine herpesvirus type 4 in dairy cows. Reprod Domest Anim 2017;52 (1):115–21.
[101] Gür S, Dog˘an N. The possible role of bovine herpesvirus type-4 infection in cow infertility. Anim Sci J 2010;81(3):304–8.
[102] Donofrio G, Herath S, Sartori C, Cavirani S, Flammini CF, Sheldon IM. Bovine herpesvirus 4 is tropic for bovine endometrial cells and modulates endocrine function. Reproduction 2007;134(1):183–97.
[103] Chanrot M, Blomqvist G, Guo Y, Ullman K, Juremalm M, Bage R, et al. Bovine herpes virus type 4 alters TNF-a and IL-8 profiles and impairs the survival of bovine endometrial epithelial cells. Reprod Biol 2017;17(3):225–32.
[104] Donofrio G, Ravanetti L, Cavirani S, Herath S, Capocefalo A, Sheldon IM. Bacterial infection of endometrial stromal cells influences bovine herpesvirus 4 immediate early gene activation: a new insight into bacterial and viral interaction for uterine disease. Reproduction 2008;136 (3):361–6.
[105] Morán PE, Pérez SE. Odeón AC, Verna AE. Bovine herpesvirus 4 (BoHV-4): general aspects of the biology and status in Argentina. Rev Argent Microbiol 2015;47(2):155–66. Spanish.
[106] Jacca S, Franceschi V, Colagiorgi A, Sheldon M, Donofrio G. Bovine endometrial stromal cells support tumor necrosis factor alpha-induced bovine herpesvirus type 4 enhanced replication. Biol Reprod 2013;88 (5):135.
[107] Donofrio G, Capocefalo A, Franceschi V, Price S, Cavirani S, Sheldon IM. The chemokine IL8 is up-regulated in bovine endometrial stromal cells by the BoHV-4 IE2 gene product, ORF50/Rta: a step ahead toward a mechanism for BoHV-4 induced endometritis. Biol Reprod 2010;83(6):919–28.
[108] Tebaldi G, Jacca S, Montanini B, Capra E, Rosamilia A, Sala A, et al. Virusmediated metalloproteinase 1 induction revealed by transcriptome profiling of bovine herpesvirus 4-infected bovine endometrial stromal cells. Biol Reprod 2016;95(1):12.
[109] Wathes DC, Cheng Z, Fenwick MA, Fitzpatrick R, Patton J. Influence of energy balance on the somatotrophic axis and matrix metalloproteinase expression in the endometrium of the postpartum dairy cow. Reproduction 2011;141 (2):269–81.
[110] Faveeuw C, Preece G, Ager A. Transendothelial migration of lymphocytes across high endothelial venules into lymph nodes is affected by metalloproteinases. Blood 2001;98(3):688–95.
[111] Fischer M, Hoffmann B, Goller KV, Höper D, Wernike K, Beer M. A mutation 'hot spot' in the Schmallenberg virus M segment. J Gen Virol 2013;94(Pt 6):1161–7.
[112] Wernike K, Hoffmann B, Beer M. Schmallenberg virus. Dev Biol 2013;135: 175–82.
[113] Martinelle L, Poskin A, Dal Pozzo F, De Regge N, Cay B, Saegerman C. Experimental infection of sheep at 45 and 60 days of gestation with Schmallenberg virus readily led to placental colonization without causing congenital malformations. PLoS ONE 2015;10(9):e0139375.
[114] Wernike K, Holsteg M, Schirrmeier H, Hoffmann B, Beer M. Natural infection of pregnant cows with Schmallenberg virus—a follow-up study. PLoS ONE 2014;9(5):e98223.
[115] Afonso A, Abrahantes JC, Conraths F, Veldhuis A, Elbers A, Roberts H, et al. The Schmallenberg virus epidemic in Europe—2011–2013. Prev Vet Med 2014;116(4):391–403.
[116] Wüthrich M, Lechner I, Aebi M, Vögtlin A, Posthaus H, Schüpbach-Regula G, et al. A case-control study to estimate the effects of acute clinical infection with the Schmallenberg virus on milk yield, fertility and veterinary costs in Swiss dairy herds. Prev Vet Med 2016;126:54–65.
[117] Varela M, Schnettler E, Caporale M, Murgia C, Barry G, McFarlane M, et al. Schmallenberg virus pathogenesis, tropism and interaction with the innate immune system of the host. PLoS Pathog 2013;9(1):e1003133.
[118] Veldhuis AM, Santman-Berends IM, Gethmann JM, Mars MH, Van Wuyckhuise L, Vellema P, et al. Schmallenberg virus epidemic: impact on milk production, reproductive performance and mortality in dairy cattle in the Netherlands and Kleve District, Germany. Prev Vet Med 2014;116 (4):412–22.
[119] Lechner I, Wüthrich M, Meylan M, Van den Borne BHP, Schüpbach-Regula G. Association of clinical signs after acute Schmallenberg virus infection with milk production and fertility in Swiss dairy cows. Prev Vet Med 2017;146:121–9.
[120] Carpenter S, Wilson A, Mellor PS. Culicoides and the emergence of bluetongue virus in northern Europe. Trends Microbiol 2009;17(4):172–8.
[121] Wilson A, Mellor P. Bluetongue in Europe: vectors, epidemiology and climate change. Parasitol Res 2008;103(Suppl 1):S69–77.
[122] Dal Pozzo F, Saegerman C, Thiry E. Bovine infection with bluetongue virus with special emphasis on European serotype 8. Vet J 2009;182 (2):142–51.
[123] Nusinovici S, Seegers H, Joly A, Beaudeau F, Fourichon C. Quantification and at-risk period of decreased fertility associated with exposure to bluetongue

virus serotype 8 in naïve dairy herds. J Dairy Sci 2012;95(6):3008–20.
[124] Osburn BI. The impact of bluetongue virus on reproduction. Comp Immunol Microbiol Infect Dis 1994;17(3–4):189–96.
[125] Uhaa IJ, Riemann HP, Thurmond MC. Franti CE. A cross-sectional study of bluetongue virus and Mycoplasma bovis infections in dairy cattle: II. The association between a positive antibody response and reproduction performance. Vet Res Commun 1990;14(6):471–80.
[126] Méroc E, Herr C, Verheyden B, Hooyberghs J, Houdart P, Raemaekers M, et al. Bluetongue in Belgium: episode II. Transbound Emerg Dis 2009;56(1–2):39–48.
[127] Santman-Berends IM, Hage JJ, van Rijn PA, Stegeman JA, Van Schaik G. Bluetongue virus serotype 8 (BTV-8) infection reduces fertility of Dutch dairy cattle and is vertically transmitted to offspring. Theriogenology 2010;74 (8):1377–84.
[128] Bowen RA, Howard TH, Elsden RP, Seidel GE. Bluetongue virus and embryo transfer in cattle. Prog Clin Biol Res 1985;178:85–9.
[129] Vandaele L, Wesselingh W, De Clercq K, De Leeuw I, Favoreel H, Van Soom A, et al. Susceptibility of *in vitro* produced hatched bovine blastocysts to infection with bluetongue virus serotype 8. Vet Res 2011;42(1):14.
[130] Ratinier M, Shaw AE, Barry G, Gu Q, Di Gialleonardo L, Janowicz A, et al. Bluetongue virus NS4 protein is an interferon antagonist and a determinant of virus virulence. J Virol 2016;90(11):5427–39.
[131] Usman T, Hadlich F, Demasius W, Weikard R, Kühn C. Unmapped reads from cattle RNAseq data: a source for missing and misassembled sequences in the reference assemblies and for detection of pathogens in the host. Genomics 2017;109(1):36–42.