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PARAMEDIK VETERINER MAHIR

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Menilai Kualitas Embrio Sapi Berasal dari Oosit yang Ditekankan Secara Metabolik Selama Pematangan Menggunakan TUNEL

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ABSTRAK

Penelitian saat ini bertujuan untuk menilai rasio sel apoptosis (ACR) melalui pewarnaan TUNEL pada embrio sapi yang diproduksi secara in vitro dari oosit yang matang dalam kondisi stres dengan peningkatan konsentrasi asam lemak non-esterifikasi (NEFAs). Kondisi maturasi dalam penelitian ini menyerupai situasi di lingkungan mikro oosit sapi perah laktasi yang mengalami stres metabolik selama periode post-partum di mana keseimbangan energi negatif terjadi. Oosit secara in vitro dimatangkan di bawah kadar NEFA yang tinggi selama 24 jam dalam media maturasi bebas serum. Zigot yang diperoleh dikultur dalam cairan saluran telur sintetik dengan 5% FCS selama delapan hari. Tahapan blastokista dari masing-masing kelompok perlakuan dinilai dan dievaluasi kualitasnya dengan menentukan ACR melalui pewarnaan TUNEL. Kehadiran asam palmitat atau stearat pada konsentrasi tinggi selama pematangan oosit meningkatkan ACR, sedangkan asam oleat tidak memiliki efek yang signifikan. Hasil penelitian ini menyimpulkan bahwa lingkungan mikro oosit yang dikompromikan oleh stresor metabolik seperti konsentrasi NEFAs yang tinggi yang merupakan situasi selama keseimbangan energi negatif yang terjadi post partum pada sapi perah dapat menurunkan kualitas embrio praimplantasi yang ditunjukkan oleh kejadian apoptosis.

PERKENALAN

Memberproduksi tinggi dihasilkan dari keseimbangan Stresor etabolik selama periode post partum pada sapi perah energi negatif dan konsekuensi yang terjadi selama periode ini. Stresor metabolik ini sangat luas dan mencakup banyak biokimia dan adaptasi metabolik dalam darah dan cairan folikel (FF). Stresor metabolik ini mungkin termasuk peningkatan konsentrasi asam lemak non-esterifikasi (NEFA) dalam lingkungan mikro oosit yang sedang tumbuh (yaitu cairan folikel) (Shehab-El-Deenet al., 2010). Inan invitromodel ketika NEFAs, seperti asam palmitat dan stearat, ditambahkan ke media pematangan oosit dengan konsentrasi yang sama terkait dengan keseimbangan energi negatif mengakibatkan kualitas embrio menurun (Shehab-El-Deenet al., 2009). Di daerah tropis dan subtropis, suhu lingkungan yang tinggi selama musim panas adalah ., 1993;Shehab-El-Deenet al., 2010). Stres panas musim panas penyebab utama subfertilitas sapi perah postpartum (Ealyet al memperburuk situasi keseimbangan energi negatif dan NEFAs terkait yang meningkat (Shehab-El-Deenet al., 2010). Pada tahap awal laktasi, sapi laktasi tinggi lebih rentan terhadap suhu lingkungan yang tinggi, karena produksi panas metabolisme yang dipercepat.Blackshaw dan Blackshaw, 1994). Oleh karena itu, jika oosit yang sedang tumbuh mengalami kondisi stres selama proses perkembangannya, kualitasnya akan terpengaruh secara negatif dan selanjutnya perkembangan embrionik.Butler, 2003). Beberapa dari kondisi stres ini termasuk perubahan biokimia dalam lingkungan mikro oosit yang terkait dengan keseimbangan energi negatif pascapersalinan.Leroyet al., 2004; Shehab-El-Deenet al., 2010). Kondisi stres yang hadir dalam lingkungan mikro oosit memiliki efek akhir pada kehamilan, persalinan dan perkembangan pasca kelahiran.Greve dan Callesen, 2005). Adaptasi biokimia selama awal laktasi pada sapi perah laktasi tinggi dapat menjadi morbid dan oleh karena itu dapat mengganggu fertilitas sapi.Butler dan Smith, 1989;Leroyet al., 2004; Shehab-El-Deenet al., 2010;Rodneyet al., 2018). Diubah

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tingkat asam lemak non-esterifikasi (NEFAs) di FF telah dikaitkan dengan perubahan kualitas oosit (Leroyet al. 2004;Shehab-El-Deenet al., 2010). Konsentrasi NEFA yang tinggi selama periode keseimbangan energi negatif (NEB) pada sapi perah laktasi tinggi telah dikaitkan dengan penurunan kesuburan yang dipelajari secara ekstensif (Robinson 1999;Rukkwamsuket al., 1999;Vanholderet al., 2005; Shehab-El-Deenet al., 2010). Asumsi ini telah dibuktikan dengan penambahan NEFAs, seperti asam oleat (OA), asam palmitat (PA) dan asam stearat (SA) pada konsentrasi, yang berlaku di FF selama NEB hingga kondisi pematangan oosit protokol produksi embrio.in vitrodalam sapi. Pemasukan asam lemak jenuh ke media maturasi oosit sapi memiliki efek merusak yang jelas pada kualitas oosit dan kompetensi perkembangan, sedangkan OA tak jenuh tunggal tidak berpengaruh.Leroyet al., 2005; Shehab-El-Deenet al., 2010). Penilaian kompetensi embrio sapi yang diperoleh dari oosit yang mengalami kondisi stres menjadi sangat penting dalam program transfer embrio yang digunakan untuk menghindari efek negatif stres panas pada sapi perah dan tujuan penelitian (Vandaele et al., 2007). Teknik terminal deoxynucleotidyl transferase mediated dUTP nick end labeling (TUNEL) digunakan untuk menilai kualitas embrio preimplantasi sapi dengan mendeteksi apoptosis sebagai rasio sel apoptosis (ACR) dan karenanya fragmentasi DNA (Spanoet al., 2000;Paula-Lopes dan Hansen, 2002).

Penelitian saat ini bertujuan untuk menilai kualitas embrio praimplantasi sapi yang diperoleh dari oosit yang terpapar konsentrasi NEFAs yang tinggi selama pematangan in vitro melalui pewarnaan TUNEL untuk menentukan kejadian apoptosis dan karenanya kualitas embrio.

BAHAN DAN METODE

In vitroproduksi embrio

Embrio sapi diproduksi secara in vitro seperti yang dijelaskan sebelumnya (Shehab-El-Deenet al., 2009). Secara singkat, ovarium sapi yang disembelih dikumpulkan dan diproses dalam waktu 2 jam sejak penyembelihan. Ovarium, setelah menghilangkan mesovaria, dibilas berkali-kali dalam garam fisiologis hangat yang mengandung kanamisin (25mg/m2). hanya folikel berdiameter berkisar antara 4 dan 8 yang diaspirasi

In vitropematangan

Oosit yang baik berdasarkan kenampakan dan lapisan sel kumulus dikultur dalam kondisi maturasi bebas serum pada kelompok 60 oosit per sumur dalam 500 µL buffer bikarbonat termodifikasi TCM199 dengan Earle's dan glutamin dan dilengkapi dengan murine epidermal growth factor (EGF) (20 ng/mL) untuk 22 jam pada suhu 38,5°C dalam 5% CO_2 di udara.

In vitropemupukan

Oosit dicuci dan dipindahkan ke media fertilisasi in vitro 500 µL IVF-TALP (60 oosit/sumur) yang terdiri dari larutan Tyrode buffer bikarbonat, dengan BSA (6 mg/mL) dan heparin (25 µg/mL). Semen sapi beku yang dicairkan dari sapi jantan yang sama dipisahkan dengan gradien kepadatan Percoll (45 dan 90%, Pharmacia, Uppsala, Swedia) dan dicuci. Konsentrasi sperma disesuaikan dalam IVF-TALP. Spermatozoa sapi ditambahkan ke dalam sumur berisi oosit dalam IVF-TALP pada konsentrasi akhir 10^6spermatozoa/mL. Oosit yang diinseminasi diinkubasi selama 20-24 jam pada suhu 38,5°C dalam 5% CO_2 di udara.

In vitrobudaya

Kemungkinan zigot menjadi sasaran pusaran untuk menyingkirkan sel kumulus dan spermatozoa. Oosit yang dibuahi dicuci beberapa kali dan dipindahkan ke SOFaa yang dilengkapi dengan 5% FCS dan dikultur dalam 50 µL tetesan SOFaa dalam kelompok 25 zigot per sumur di bawah minyak mineral selama 8 hari dalam kondisi oksigen rendah; 5% O_2, 5% CO_2 dan 90% N_2.

Penambahan asam lemak non-esterifikasi (NEFAs) ke media pematangan

Asam lemak non-esterifikasi yang dipelajari; asam oleat (OA), asam palmitat (PA) atau asam stearat (SA) dilarutkan dalam etanol absolut. Ketiga asam lemak diuji dalam 3 ulangan (1800 oosit), selain kelompok kontrol negatif dan positif. Media kontrol terdiri dari media maturasi normal tanpa NEFAs atau ehtanol (kontrol negatif) atau dengan etanol absolut (kontrol positif) (Leroy et al., 2005).

Deteksi apoptosis

Termasuk keluarga sapiin vitromenghasilkan blastokista pada hari ke delapan setelah inseminasi dari masing-masing kelompok perlakuan dilakukan pewarnaan TUNEL (In Situ Cell Detection kit, Boehringer, Mannheim, Jerman) untuk deteksi apoptosis menurutGjørretet al. (2003). Secara singkat, blastokista yang dihasilkan pada masing-masing kelompok dicuci dalam phosphate buffer saline (PBS) dua kali selama 2 menit pada suhu 37°C dan kemudian difiksasi dalam paraformaldehyde 4% dan disimpan hingga pewarnaan. Blastokista di permeabilisasi dalam Triton X-100 (0,5% dalam PBS) selama 1 jam pada suhu kamar dalam gelap. Blasotcyst TUNEL positif dan TUNEL negatif diinkubasi selama 1 jam dalam gelap pada suhu 37°C dalam DNase (50 Unit/mL dalam PBS). Langkah Durig DNase, blastokista dari kelompok lain disimpan dalam polivinil pirolidon (PVP) dalam PBS pada suhu kamar. Untuk larutan TUNEL, blastokista dari semua kelompok perlakuan dan kontrol positif TUNEL diinkubasi dalam fluorescein dUTP dan terminal deoxynucleotidyl transferase dalam gelap selama satu jam (37°C). Sementara itu,

Blastokista kontrol TUNEL-negatif tidak dikenai transferase dan diinkubasi hanya dalam campuran nukleotida. Setelah itu, semua blastokista diinkubasi dalam RNase (50µg/ml dalam PBS) selama 1 jam dalam gelap pada suhu kamar. Selanjutnya, semua blastotcyst dikenai 0,5% propidium iodide (PI) untuk pewarnaan inti selama satu jam pada suhu kamar. Akhirnya, blastokista dicuci dengan cepat di PVP di PBS dan dipasang di tetesan 1, 4-diazabicyclo (2.2.2) oktan (DABCO) pada slide dengan jembatan vaseline. Blastomer yang TUNEL Positif dibaca dengan mikroskop fluoresensi. Propidium iodida membantu mengidentifikasi nuklei yang normal, terkondensasi atau terfragmentasi dan menghitung jumlah sel total, sementara nuklei TUNEL-positif tampak hijau kekuningan, terkondensasi atau terfragmentasi.

Rasio sel apoptosis dinilai sebagai persentase blastomer TUNEL-positif baik dalam massa sel bagian dalam atau dalam trofektoderm.

Analisis statistik

Persentase sel-sel apoptosis pada blastokista dari kelompok perlakuan yang berbeda dianalisis menggunakan analisis varians model campuran dengan kelompok sebagai faktor tetap dan replikasi sebagai faktor acak. Model yang sama digunakan untuk mengevaluasi persentase blastokista pada 8 dpi. Untuk semua analisis, perbedaan dianggap signifikan secara statistik pada tingkat 5%. Analisis statistik dilakukan dalam SPSS versi 14.00

HASIL

Tidak ada perbedaan signifikan yang dapat dideteksi dalam hasil blastokista atau hasil blastokista yang diperluas pada 8 dpi (Tabel I). Namun, penambahan ketiga asam lemak tersebut ke media pematangan secara signifikan menurunkan jumlah sel total dan jumlah sel trofektoderm dari embrio yang dihasilkan (P<0,01) (Gambar 1). Hasil yang sama ditemukan pada massa sel bagian dalam untuk asam oleat dan palmitat tetapi tidak untuk asam stearat dibandingkan dengan kelompok kontrol negatif. Ketika apoptosis pada blastokista yang diperluas dinilai (Gambar 2), ditemukan bahwa asam stearat dan palmitat selama pematangan meningkatkan ACR dalam massa sel bagian dalam pada embrio yang dihasilkan (P<0,01). Namun, pada trofektoderm, asam palmitat hanya meningkatkan kejadian apoptosis (P<0,01). Efek asam palmitat yang sama ditemukan pada jumlah sel total (P<0,01). Sedangkan penambahan etanol selamain vitro pematangan tidak mempengaruhi ACR dalam menghasilkan embrio dalam penelitian ini.

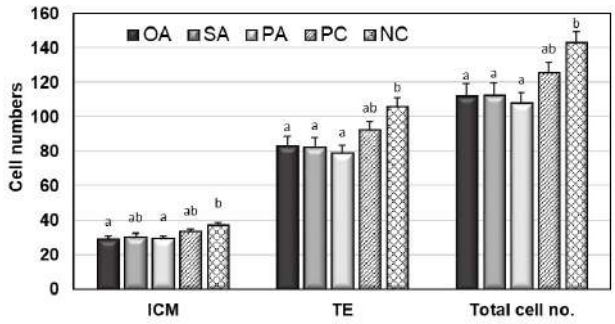
DISKUSI

Studi saat ini menguji efek kondisi pematangan oosit pada kualitas embrio selanjutnya. Itu terkenal bahwa oosit dengan kualitas rendah menyebabkan embrio berkembang lambat dan tingginya insiden apoptosis selama perkembangan embrionik praimplantasi (Vandaeleet al., 2007). Asam lemak nonesterifikasi telah banyak dilaporkan menginduksi apoptosis pada sel granulosa dan kumulus dari folikel ovarium yang sedang berkembang. Selain itu, NEFA hadir dalam lingkungan mikro oosit atau dalam media pematangan dapat berdampak negatif pada kualitas oosit dan kompetensi perkembangan. Selain itu, tingkat NEFA yang tinggi menentukan sel-sel folikel karena mempengaruhi proses steroidogenesis dan proliferasi.Leroyet al., 2004;2005; Vanholderet al., 2005;Shehab-El-Deenet al., 2010; Baddelaet al., 2020). Selain itu, NEFA juga dapat berkontribusi pada masalah ovarium polikistik karena dapat meningkatkan regulasi sel Sertoli marker-9, faktor transkripsi androgenik dan menurunkan regulasi pasangan estrogeniknya dalam sel grnaulosa.Yenuganti dan Vanselow, 2017). Dengan demikian, menilai kualitas embrio sapi yang dihasilkan dari oosit yang mengalami tingkat NEFAs tinggi selama pematangan menjadi pendekatan penting untuk menentukan hasil fertilitas pada sapi perah berproduksi tinggi selama keseimbangan energi negatif atau stres panas yang terkait dengan stres metabolik. Terjadinya apoptosis pada embrio sapi yang diproduksi secara in vitro dapat dideteksi pada saat aktivasi genom embrionik (yaitu sekitar tahap delapan sel) menggunakan TUNEL (Byrneet al., 1999; Matwee et al., 2000;Gjørretet al., 2003). Telah ditunjukkan dengan baik bahwa peningkatan konsentrasi asam lemak non-esterifikasi dalam lingkungan mikro oosit menghambat kualitas oosit dan juga memiliki konsekuensi pada kualitas embrio dugaan. Pada stadium morula dan blastokista, blasotmer tertentu mengalami apoptosis sebagai mekanisme fisiologis untuk menghilangkan kelemahan.

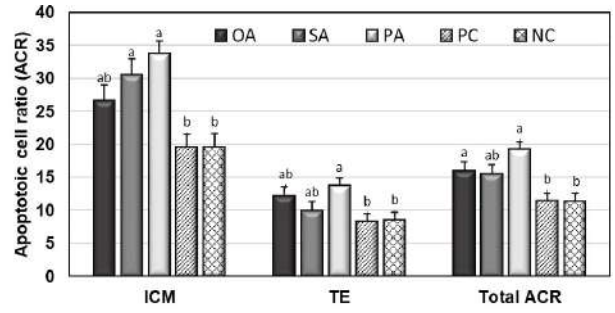
Tabel I. Hasil blastokista dan perluasan blastokista (rata-rata ± SE) pada hari ke 8 pasca inseminasi oosit sapi matang dengan adanya asam palmitat (C16:0), asam stearat (C18:0) atau asam oleat (C18:1). Kontrol negatif adalah media maturasi tanpa asam lemak atau etanol dan kelompok kontrol positif adalah media maturasi dengan penambahan etanol absolut.

Perlakuan kelompok	Tidak. berbudaya oosit	% blastokista	% Diperluas blastokista
Asam palmitat	318	28,15±4,34	17,02±2,58
Asam stearat	318	27,2±3,89	16,02±2,3
Asam oleat	333	32,73±3,9	18,15±2,4
Kontrol negatif	314	30,46±2,75	15,76±1,63
Kontrol positif	300	29,89±2,62	16,46±1,55

Persentase blastokista dan perluasan blastokista dihitung dari oosit yang dikultur.



Gambar 1. Jumlah sel (rata-rata ± SE) massa sel bagian dalam (ICM), trofektoderm (TE) dan jumlah sel total pada embrio sapi (8 dpi) yang berasal dari oosit yang dimatangkan baik dalam asam oleat (OA) (C18:1) , asam stearat (SA) (C18:0) atau asam palmitat (PA) (C16:0). Kontrol negatif (NC) adalah media pematangan dan kelompok kontrol positif (PC) adalah media pematangan dengan penambahan etanol murni.A, BBatangan yang memuat superskrip berbeda berbeda dalam setiap kategori; massa sel dalam (ICM), trofektoderm (TE) atau jumlah sel blastokista total(P<0,01).



Gambar 2. Rasio sel apoptosis (ACR) (rata-rata ± SE) dalam massa sel bagian dalam (ICM) dan trofektoderm (TE) embrio sapi (8 dpi) yang berasal dari oosit yang dimatangkan baik dalam asam palmitat (PA) (C16:0) , asam stearat (SA) (C18:0) atau asam oleat (OA) (C18:1). Kontrol negatif (NC) adalah media pematangan dan kelompok kontrol positif (PC) adalah media pematangan dengan penambahan etanol murni.a, bBatangan yang memuat superskrip berbeda berbeda dalam setiap kategori; massa sel dalam (ICM), trofektoderm (TE) atau jumlah sel blastokista total (P<0,01).

sel yang rusak untuk menyeimbangkan perbanyakan dan kematian sel, lebih jauh lagi, kematian sel yang terprogram memainkan peran penting untuk menyapu balstomer dengan genom yang diubah dari perkembangan lebih lanjut, yang sangat penting dalamin vitro blastokista yang dihasilkan mengalami kondisi stres (Ramos-Ibeas et al ., 2020). Dengan demikian, kejadian apoptosis pada embrio yang dihasilkan dari oosit yang mengalami kondisi stres tampaknya merupakan mekanisme adaptif untuk memastikan bahwa sel-sel yang tidak sehat dan embrio awal tidak mengalami kemajuan dalam perkembangan, menghindari efek merugikan jangka panjang.

Sebenarnya, baik PA maupun SA menyebabkan peningkatan ACR yang signifikan pada massa sel dalam dibandingkan dengan kelompok kontrol baik kelompok kontrol positif (etanol) maupun kelompok kontrol negatif. Namun, tidak ada perbedaan yang signifikan antara ketiga asam lemak yang diteliti pada ACR baik pada ICM maupun pada trophobalst. Peningkatan ACR pada ICM, mungkin disebabkan oleh perubahan kualitatif dan⁄ atau kuantitatif pada lipid sitoplasma atau membran sel. Ketika lipid intraseluler dikeluarkan dari embrio babi, mereka menjadi lebih toleran terhadap cedera kriogenik, yang menunjukkan bahwa lipid ini dapat menghambat kualitas dan perkembangan embrio. Nagashimaet al., 1995). Lebih-lebih lagi,Abeet al. (2002) membuktikan bahwa akumulasi lipid dalam embrio dapat merusak kualitas dan cryotolerance mereka (Abeet al., 2002).

Asam lemak dalam lingkungan mikro oosit dapat terakumulasi di dalam oosit dan berpotensi mengubah kandungan dan komposisi lipid oosit.Kimet al., 2001; Adamiak et al., 2005;Leroyet al., 2008).Kimet al. (2001) menyatakan bahwa PA, OA dan SA adalah tiga asam lemak yang dominan pada oosit sapi. Selain itu, maturasi in vitro oosit sapi dengan adanya trigliserida serum dan kadar kolesterol total yang diubah, yang terbukti bahwa lipid dan asam lemak dapat dimasukkan ke dalam sitoplasma oosit.Kimet al., 2001). Temuan mereka menunjukkan bahwa kedua kondisi maturasi, morfologi oosit dan kriopreservasi, dapat mempengaruhi komposisi asam lemak pada oosit sapi.Shehab-El-Deenet al. (2009)mengkonfirmasi bahwa paparan oosit sapi selama pematangan hingga konsentrasi NEFA yang penuh tekanan memiliki efek bawaan pada kualitas embrio. Namun, masih belum diketahui apakah apoptosis terlibat dalam kualitas embrio rendah yang diamati. Lebih khusus lagi, asam palmitat mungkin merupakan elemen negatif yang penting dalam hal ini (Van Soomet al., 2001). Telah ditunjukkan dengan baik bahwa asam lemak dalam media kultur dapat diambil oleh embrio untuk digunakan untuk pembaharuan lipid membrannya (Pratt, 1980); oleh karena itu, setiap perubahan dalam membran sel selama pematangan oosit dapat memengaruhi perkembangan embrio. Namun,Matweeet al. (2000)menyimpulkan bahwa seiring perkembangan embrionik, embrio sapi mengembangkan resistensi terhadap apoptosis. Selain itu, sebelumnya telah ditunjukkan bahwa SA dan PA menginduksi apoptosis pada sel kumulus, yang pasti mempengaruhi pematangan oosit melalui gap junction dan mungkin juga perkembangan embrio dapat dipengaruhi secara negatif. Kemungkinan jalur dimana asam lemak menginduksi apoptosis adalah melalui mempengaruhi transduksi sinyal, karena mereka terlibat dalam beberapa jalur transduksi sinyal. Baik asam stearat dan asam linoleat terlibat dalam stimulasi protein kinase C yang menyebabkan apoptosis.Yuet al., 2001;Eitelet al., 2003). Hasil penelitian saat ini menyimpulkan bahwa pematangan in vitro oosit sapi pada tingkat stres PA dan SA dapat terjadi

efek carry-over pada kualitas embrio, yang menyebabkan peningkatan apoptosis pada massa sel bagian dalam. Namun, PA hanya meningkatkan apoptosis pada trofektoderm. Namun, penelitian lebih lanjut masih diperlukan untuk menjelaskan mekanisme di mana NEFA menginduksi apoptosis.

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Artikel Penelitian

Penyebaran Virus Penyakit Kulit Benjolan di Asia Tenggara: Wawasan dari Pengawasan

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Penyakit kulit kental (LSD) adalah penyakit lintas batas yang dapat dilaporkan, menyebabkan dampak ekonomi dan kesejahteraan yang besar pada sapi. Sebelum Oktober 2020, LSD belum pernah dilaporkan di Asia Tenggara; namun, pada 5 Oktober 2020, Vietnam melaporkan kasus pertama di wilayah tersebut. Studi ini bertujuan untuk menyelidiki penyebaran awal virus LSD (LSDV) pada sapi di seluruh Asia Tenggara antara Oktober 2020 dan Oktober 2021. Data wabah LSD diakses dari database World Organization for Animal Health (WOAH) World Animal Health Information System (WAHIS). dan dianalisis untuk menyelidiki penyebaran ini melalui kurva epidemi, peta penyakit, pengelompokan, dan statistik deskriptif. Selama periode epidemi, 866 wabah LSD dilaporkan dari enam negara Asia Tenggara, terdiri dari 1.758.923 sapi rentan, 93.465 kasus, 5.936 kematian, dan 1.117 sapi dimusnahkan. Analisis mengungkapkan penyebaran epidemi di seluruh Asia Tenggara, dengan empat puncak utama dalam jumlah kasus di seluruh Tailand dan Vietnam. Kumpulan pohon wabah yang dilaporkan diidentifikasi, dan Tailand ditemukan sebagai pusat wabah di wilayah tersebut, yang dapat mencerminkan bias pelaporan dan pelaporan yang kurang dari negara lain di Asia Tenggara. Tingkat morbiditas dan mortalitas yang tinggi dilaporkan, khususnya di Tailand, Vietnam, dan Kamboja, kemungkinan mencerminkan infeksi pada populasi naif dan kurangnya program vaksinasi yang efektif. Temuan ini berbeda dengan apa yang umumnya telah dijelaskan di bagian lain dunia. Selanjutnya, studi harus meneliti faktor risiko yang terkait dengan tingkat morbiditas dan mortalitas yang tinggi di wilayah ini.

1. Perkenalan

Penyakit kulit kental (LSD) adalah penyakit lintas batas yang dapat dilaporkan, menyebabkan dampak ekonomi dan kesejahteraan yang besar pada ternak. LSD disebabkan oleh virus penyakit kulit kental (LSDV), milik keluargaPoxviridaedan marga Capripoxvirus[1]. LSD terutama menyerang sapi, bufalo air, dan ruminansia liar; namun, beberapa laporan infeksi pada satwa liar telah dicatat [2]. Semua umur dan ras rentan terhadap penyakit ini, tetapi infeksi paling sering dilaporkan—dan yang paling parah—pada sapi muda, sapi kurus, dan pada masa laktasi puncak atau gangguan sistem imun [3]. Sementara kematian penyakit biasanya rendah (1-3%), tingkat morbiditas tinggi, rata-rata 5-45% [2, 4]. Kondisi ini ditandai dengan nodul kulit berbatas tegas berukuran 2–6 cm diameter, umumnya terdapat pada bagian leher, kaki, ekor, dan punggung [5]. Hewan yang terinfeksi secara klinis juga biasanya mengalami demam, pembesaran kelenjar getah bening, depresi, penurunan produksi susu, dan aborsi [2]. LSDV dapat bertahan hidup di lingkungan hingga 35 hari, dengan sumber utama LSDV adalah lesi kulit nekrotik, keropeng, dan darah [6]. Penularan dapat terjadi melalui arthropoda penghisap darah, seperti nyamuk danStomoxysspp., pakan dan air yang terkontaminasi, dan sekresi tubuh [7]. Peningkatan wabah dan jumlah kasus terjadi di musim panas dan selama musim hujan ketika spesies vektor melimpah, menunjukkan penyebaran virus terutama terkait dengan transmisi vektor [7, 8].

Endemik awalnya di Afrika, LSD telah menyebar di beberapa bagian Eropa melalui pergerakan hewan yang terinfeksi dan transmisi vektor, diperkuat oleh wabah terkait musiman [7, 9].

Kegigihan lingkungan LSDV dan berbagai mode penularan menciptakan tantangan bagi program pengendalian dan pencegahan di seluruh dunia. Meskipun demikian, meluasnya penggunaan vaksin hidup yang dilemahkan selama wabah Balkan (2015-2017) terbukti berhasil mengendalikan epidemi ini [10]. Selain itu, deteksi wabah dini, pemusnahan (pemusnahan ternak yang terkena dan diduga terinfeksi), dan pembatasan pergerakan ternak telah membantu program pengendalian di seluruh dunia [10]. Meskipun langkah-langkah pengendalian ini telah diterapkan di daerah endemik, LSDV baru-baru ini menyebar ke Asia, dengan laporan dari China, India, Bangladesh, dan Nepal [11, 12]. Selanjutnya, wabah LSD pertama yang dilaporkan di Asia Tenggara terjadi di Vietnam (Distrik Huu Lung, Provinsi Lang Son) pada Oktober 2020 [13]. Selama 2020-2021, penyakit ini menyebar ke lima negara Asia Tenggara lainnya: Kamboja, Laos, Malaysia, Myanmar, dan Thailand. Karena kejadian LSD baru-baru ini di Asia Tenggara, pengetahuan terkini mengenai status dan tren wabahnya di kawasan ini masih jarang. Mengingat luasnya wabah ini dan kurangnya pengetahuan seputar LSD di Asia Tenggara, penting untuk menyelidiki pola epidemiologis LSD di wilayah ini. Bersamaan dengan masalah kesejahteraan, data dari wabah sebelumnya menunjukkan LSD menjadi beban keuangan yang besar bagi produsen karena penurunan produksi susu, pembatasan perdagangan, dan biaya perawatan dan pencegahan [2, 14]. Oleh karena itu, menyelidiki tren epidemiologi LSD di Asia Tenggara dapat membantu mengurangi penyebaran lebih lanjut dan mengurangi dampak konsekuensial dari penyakit tersebut. dan Thailand. Karena kejadian LSD baru-baru ini di Asia Tenggara, pengetahuan terkini mengenai status dan tren wabahnya di kawasan ini masih jarang. Mengingat luasnya wabah ini dan kurangnya pengetahuan seputar LSD di Asia Tenggara, penting untuk menyelidiki pola epidemiologis LSD di wilayah ini. Bersamaan dengan masalah kesejahteraan, data dari wabah sebelumnya menunjukkan LSD menjadi beban keuangan yang besar bagi produsen karena penurunan produksi susu, pembatasan perdagangan, dan biaya perawatan dan pencegahan [2, 14]. Oleh karena itu, menyelidiki tren epidemiologi LSD di Asia Tenggara dapat membantu mengurangi penyebaran lebih lanjut dan mengurangi dampak konsekuensial dari penyakit tersebut. dan Thailand. Karena kejadian LSD baru-baru ini di Asia Tenggara, pengetahuan terkini mengenai status dan tren wabahnya di kawasan ini masih jarang. Mengingat luasnya wabah ini dan kurangnya pengetahuan seputar LSD di Asia Tenggara, penting untuk menyelidiki pola epidemiologis LSD di wilayah ini. Bersamaan dengan masalah kesejahteraan, data dari wabah sebelumnya menunjukkan LSD menjadi beban keuangan yang besar bagi produsen karena penurunan produksi susu, pembatasan perdagangan, dan biaya perawatan dan pencegahan [2, 14]. Oleh karena itu, menyelidiki tren epidemiologi LSD di Asia Tenggara dapat membantu mengurangi penyebaran lebih lanjut dan mengurangi dampak konsekuensial dari penyakit tersebut. pengetahuan saat ini mengenai status dan tren wabahnya di wilayah tersebut masih jarang. Mengingat luasnya wabah ini dan kurangnya pengetahuan seputar LSD di Asia Tenggara, penting untuk menyelidiki pola epidemiologis LSD di wilayah ini. Bersamaan

dengan masalah kesejahteraan, data dari wabah sebelumnya menunjukkan LSD menjadi beban keuangan yang besar bagi produsen karena penurunan produksi susu, pembatasan perdagangan, dan biaya perawatan dan pencegahan [2, 14]. Oleh karena itu, menyelidiki tren epidemiologi LSD

Tujuan dari penelitian ini adalah untuk menyelidiki dan memetakan penyebaran penyakit kulit menggumpal pada sapi di seluruh Asia Tenggara antara Oktober 2020 dan Oktober 2021, selama fase awal penyebarannya. Analisis wabah dilakukan untuk menentukan pola jumlah kasus, lokasi, waktu wabah, dan perkembangan epidemi di seluruh wilayah. Investigasi ini didasarkan pada data yang diperoleh dari database World Animal Health Information System (WAHIS) World Organization for Animal Health (WOAH).

2. Bahan-bahan dan metode-metode

2.1. Pengumpulan dan Pengelolaan Data.Lokasi dan tanggal wabah LSD yang dilaporkan di seluruh Asia Tenggara bersumber dari WOAH. Notifikasi langsung dan laporan tindak lanjut diunduh dari koleksi Animal Disease Events yang tersedia untuk umum di antarmuka WAHIS (https:// wahis.woah.org/#/home; terakhir diakses pada 15/04/2022). Antarmuka ini diakses setiap bulan dari akhir periode studi (Oktober 2021) hingga April 2022. Laporan yang ada di database pada saat itu dianggap sebagai dataset studi terakhir. Wabah LSD yang dilaporkan dalam antarmuka WAHIS dipilih jika terjadi di negara Asia Tenggara (Brunei, Myanmar, Kamboja, Timor-Leste, Indonesia, Laos, Malaysia, Filipina, Singapura, Tailand, dan Vietnam) antara 1 Oktober
2020 dan 1 Oktober 2021. Kasus LSD yang dilaporkan didiagnosis oleh pihak berwenang di setiap negara berdasarkan tanda klinis dan deteksi asam nukleat (uji PCR), serta nekropsi (di Myanmar dan Tailand). Tidak ada tambahan rincian tentang prosedur diagnostik didokumentasikan dalam data yang tersedia. Dari setiap laporan WAHIS, informasi berikut diambil: tanggal laporan, tanggal awal dan akhir wabah (jika berlaku), lokasi wabah (lintang/bujur dan menurut nama), jenis unit (desa atau peternakan), dan jumlah hewan yang rentan, kasus , kematian, dan dimusnahkan. Laporan disaring untuk memasukkan hanya sapi; laporan LSD di negara lain Bovidae(kerbau,Capricornis sumatraensis, Bos frontalis, DanBos javanicus) dikeluarkan karena jumlah laporan yang sedikit (37) dan jumlah kasus yang rendah (115). Data yang dikumpulkan diimpor ke Excel 16.0 (Microsoft, Redman WA), dan laporan digabungkan ke dalam kumpulan data (berdasarkan negara
asal) untuk analisis lebih lanjut. Pemeriksaan kesalahan dilakukan: untuk setiap entri data, nilai logika diperiksa, dan pemeriksaan manual terhadap laporan asli dari basis data WAHIS juga dilakukan.

2.2. Analisis data.Hari epidemi dihitung dengan menetapkan hari 1 untuk kasus pertama yang dilaporkan di wilayah tersebut (5 Oktober 2020), dan kemudian setiap tanggal laporan diberi nomor relatif terhadap tanggal dasar ini.

Jumlah harian kasus dan laporan wabah untuk setiap negara dihitung dan diplot untuk periode wabah, pada skala normal dan log, untuk menghasilkan kurva epidemik (Microsoft Excel 16.0). Lokasi (lintang dan bujur) wabah yang dilaporkan telah dipetakan; ini dicapai dengan menggunakan file

bentuk Asia Tenggara (DIVA-GIS, sistem koordinat geografis (GCS) WGS 1984) dalam sistem informasi geografis (ArcGIS v10.7. ESRI, Redlands, CA). Poin data untuk setiap wabah yang dilaporkan dibuat dengan menggunakan nilai lintang dan bujur yang dilaporkan. Berdasarkan hari setiap wabah dilaporkan terjadi, jalur warna (hari epidemi hijau ke merah [hari 1–361]) digunakan untuk memvisualisasikan penyebaran epidemi LSD di seluruh Asia Tenggara. Pusat rata-rata dan satu elips arah deviasi standar (ditimbang dan ditimbang berdasarkan hari epidemi dan jumlah kasus) dihitung. Alat visualisasi ini dihamparkan pada peta titik wabah yang dilaporkan untuk menggambarkan perkembangan epidemi LSD di Asia Tenggara. Pembobotan pusat rata-rata dan elips arah menggunakan hari epidemi di setiap lokasi atau jumlah kasus yang dilaporkan di setiap lokasi. Jadi, lokasi di mana LSD dilaporkan kemudian atau lebih banyak kasus dilaporkan lebih memengaruhi perkiraan pusat rata-rata dan elips arah. Dengan cara ini, apakah waktu atau intensitas wabah mempengaruhi distribusi epidemi dapat diselidiki. Selain lokasi kasus pada hari epidemi,

Analisis ruang-waktu retrospektif dilakukan (SaTScan v9.6, https://www.satscan.org/) untuk mengidentifikasi klaster yang ada dalam data yang dilaporkan WAHIS. Model Poisson diskrit (populasi berisiko) digunakan, yang mengasumsikan jumlah kasus yang dilaporkan di setiap lokasi berdistribusi Poisson, yaitu, jumlah kasus yang diharapkan di setiap lokasi sebanding dengan ukuran populasi [15].

Oleh karena itu, dalam analisis ini pembilang adalah jumlah kasus yang dilaporkan pada setiap lokasi, dan penyebut adalah jumlah sapi rentan di lokasi yang sama dalam laporan yang sama yang disampaikan kepada WAHIS. Data ini dipindai untuk kelompok lokasi dengan tingkat serangan yang tinggi. Ukuran kluster spasial maksimum ditetapkan secara sewenang-wenang menjadi 20% dari populasi yang berisiko dan ukuran kluster temporal maksimum menjadi 50% dari periode penelitian untuk mengidentifikasi kluster yang diminati. Cluster yang teridentifikasi diinterpretasikan berdasarkan rasio kasus yang diharapkan dengan yang diamati, dan signifikansi statistik dievaluasi dengan rasio kemungkinan log menggunakan simulasi Monte-Carlo dengan 999 iterasi. Cluster yang signifikan secara statistik yang diidentifikasi dipetakan (ArcGIS v10.7.ESRI, Redlands, CA) berdasarkan pusat cluster (bujur, lintang) dan radius (km).

Analisis deskriptif dilakukan dengan menggunakan Excel 16.0. Morbiditas (jumlah kasus÷hewan rentan), mortalitas (jumlah kematian÷hewan rentan), dan laju pemusnahan (jumlah pemusnahan÷hewan yang rentan) perkiraan dihitung sebagai proporsi untuk setiap laporan yang diserahkan ke WAHIS. "Culled" diartikan sebagai sapi yang dimusnahkan oleh pihak berwenang atau peternak dan dibuang karena tertular. Analisis untuk setiap negara juga mencakup jumlah wabah, angka rentan, kasus, kematian, dan pemusnahan, serta rata-rata, median, dan kisaran interkuartil (IQR) dari jumlah kasus dan hari epidemi.

3. Hasil

Antara 1 Oktober 2020 dan 1 Oktober 2021, 866 wabah LSD dilaporkan dari negara-negara Asia Tenggara ke database WAHIS (Tabel 1 dan 2). Laporan ini merinci total 1.758.923 sapi yang rentan, 93.465 kasus, 5.936 kematian, dan 1.117 sapi yang dimusnahkan (Tabel 1 dan 3). Wabah pertama kali dilaporkan dari Vietnam (5 Oktober 2020) dan Myanmar (9 November 2020), dan kemudian dari Thailand (29 Maret 2021), dan terakhir dari Malaysia (10 Mei 2021), Laos (22 Mei 2021), dan Kamboja (26 Mei 2021).

Karena jumlah kasus per laporan tidak konstan, baik kasus maupun laporan diplot untuk lebih memahami epidemi. Wabah yang dilaporkan di seluruh Asia Tenggara menggambarkan penyebaran epidemi, dengan empat puncak utama dalam jumlah kasus (Gambar 1 dan 2). Puncak pertama terjadi pada hari ke-74 di Vietnam, dan tiga puncak lainnya terjadi pada hari ke-220, 238, dan 246 di Tailand (Gambar 1). Kurva epidemi menunjukkan Tailand telah mengalami epidemi LSD dengan periode wabah dan kasus yang terkonsentrasi, sementara negara lain (Kamboja dan Malaysia) mengalami wabah yang lebih lama dengan lebih sedikit kasus yang terjadi dalam periode waktu yang lebih lama (Gambar 1 dan 2). Sebagian besar wabah (N 533), ternak rentan (N 1.738.566), kasus (N 78.968), dan kematian (N 5.874) terjadi di Tailand, pusat wabah Asia Tenggara (Tabel 1–3; Gambar 3). Sekunder setelah Tailand, Vietnam mengalami jumlah kasus tertinggi berikutnya (N 12.703), diikuti oleh Kamboja (N 824). Kurva epidemi spesifik negara ditunjukkan pada Gambar Tambahan A dan B. Seperti yang diharapkan, semua rata-rata pusat dihitung (tidak tertimbang, kasus, dan hari epidemi tertimbang) terletak di Tailand, dengan pusat kasus di timur laut dan pusat hari tidak tertimbang dan epidemi terletak berdekatan dan di selatan di Tailand (Gambar 3). Arah sebaran selama masa penelitian adalah utara ke selatan dengan nilai 3,8° rotasi. Jika ditimbang dengan hari epidemi (1–361), arah penyebarannya sangat mirip (2.3°rotasi) ke analisis tanpa bobot, tetapi ketika ditimbang dengan jumlah kasus wabah yang dilaporkan (0–11520), ada pergeseran timur laut yang nyata (41,1°rotasi), menunjukkan dampak yang lebih besar dari LSD di wilayah timur Tailand selama bulan-bulan awal epidemi ini (Gambar 3).

Rata-rata hari wabah mengikuti pola yang sama dengan penyebaran LSD di seluruh Asia Tenggara (Tabel 2). Myanmar hanya melaporkan satu wabah selama epidemi Asia Tenggara, dan Laos melaporkan sembilan wabah. Epidemi di Laos dan Myanmar hanya memiliki sedikit kasus, dan tidak lama kemudian, mereka secara resmi menandai wabah di negara mereka telah teratasi, tanpa kasus lebih lanjut sejak kejadian awal dilaporkan. Sebagian besar kasus di Vietnam terjadi pada satu hari epidemi (74), diikuti dengan periode waktu yang substansial tanpa laporan penyakit. Selanjutnya, pada hari ke 293 periode epidemi, kasus muncul kembali, dengan sedikit peningkatan jumlah kasus yang dilaporkan menjelang akhir periode penelitian. Malaysia dan Kamboja melaporkan wabah LSD di akhir epidemi, dengan jumlah kasus terus meningkat menjelang akhir periode penelitian.

Cluster utama pohon diidentifikasi dengan analisis data spasial dan dianggap signifikan secara statistik. Kluster utama berpusat di Tailand timur tetapi termasuk Laos dan terjadi antara 13 Mei dan 30 Juni 2021. Dalam kluster ini (radius 125 km), terdapat rasio kasus yang diamati terhadap perkiraan sebesar 9,57 (P<0.001) (Gambar 4). Kluster sekunder terjadi di Tailand tengah dan terjadi dalam jangka waktu yang lebih lama, antara 21 April 21 dan 5 Juli 2021. Jari-jari kluster ini lebih besar (195 km), dengan rasio pengamatan terhadap ekspektasi sebesar 4,91 (P<0.001) (Gambar 4). Kluster tersier dan terkecil terjadi di timur laut Tailand antara 17 April dan 13 Mei 2021. Dalam kluster ini (radius 67 km), terdapat rasio kasus yang diamati terhadap perkiraan sebesar 11,06 (P<0.001) (Gambar 4).

Secara keseluruhan, di enam negara, morbiditas kasus adalah 20,9%, mortalitas kasus 2,7%, dan tingkat kematian 0,7% (Tabel 1). Morbiditas tertinggi di Tailand (37,1%) dan Kamboja (22,4%), diikuti oleh Malaysia (19,5%), Laos (19,1%), Vietnam (18,1%), dan Myanmar (9,5%) (Tabel 1). Kematian tertinggi di Vietnam (7,7%) dan Tailand (7,3%), sementara negara-negara lain memiliki tingkat kematian kurang dari 1,1% (Tabel 1). Tingkat pemusnahan tertinggi di Vietnam (4,4%), diikuti oleh Tailand (0,03%), dengan negara lain melaporkan tidak ada sapi yang dimusnahkan (Tabel 1).

4. Diskusi

Studi ini memberikan gambaran epidemiologi LSDV di seluruh Asia Tenggara pada tahun 2020-2021, melalui

Meja1: Ringkasan statistik kasus penyakit kulit menggumpal (LSD), morbiditas, dan mortalitas di Tailand, Malaysia, Kamboja, Vietnam, Laos, dan Myanmar, dilaporkan ke World Organization for Animal Health (WOAH) World Animal Health Information System (WAHIS) dari 1 Oktober 2020 hingga 1 Oktober 2021.

Parameter	Thailand	Malaysia	Kamboja	Vietnam	Laos	Myanmar	Rata-rata	Total
Jumlah laporan	553	267	21	15*	9	1	144.33	866
Jumlah sapi rentan Jumlah	1738566	11271	3907	3098	2018	63	293153.83	1758923
kasus	78968	595	824	12703	369	6	15577.5	93465
Jumlah kematian	5874	1	13	48	0	0	989.33	5936
Nomor dimusnahkan	20	0	0	1097	0	0	186.17	1117
Rata-rata morbiditas (%)	37.1	19.5	22.4	18.1	19.1	9.52	20.95	—
Morbiditas minimum (%)	0,001	0,20	13.33	3.76	14.91	9.52	6.95	—
Morbiditas maksimum (%)	100	100	41.67	48	20	9.52	53.20	—
Rata-rata kematian (%)	7.3	0,07	1.1	7.7	0	0	2.68	—
Kematian minimum (%)	0	0	0	0	0	0	0	—
Kematian maksimum (%)	100	20	6.67	53.57	0	0	30.04	—
Rata-rata dimusnahkan (%)	0,03	0	0	4.4	0	0	0,73	—
Minimal dimusnahkan (%)	0	0	0	0	0	0	0	—
Dimusnahkan maksimum (%)	14.08	0	0	15.09	0	0	4.86	—

Jumlah total laporan (N=866), jumlah sapi rentan (N=1758923), jumlah kasus (N=93465), jumlah kematian (N=5936), dan jumlah yang dimusnahkan (N=1117) dilaporkan untuk setiap negara. Morbiditas dan mortalitas dihitung sebagai jumlah kasus÷jumlah ternak rentan dan jumlah kematian÷jumlah sapi yang rentan, masing-masing. Proporsi yang dimusnahkan dihitung sebagai jumlah yang dimusnahkan÷jumlah sapi yang rentan. Rata-rata dihitung dan dilaporkan di semua negara (N=6). Data diambil dari WOAH WAHIS (https://wahis.woah.org/#/home).*Vietnam hanya secara resmi melaporkan 15 wabah; namun, 2 wabah mengandung sub-wabah yang mencakup sebagian besar kasus (wabah 84273 memiliki 205 sub-wabah, mencakup 11.520 kasus dan wabah 84272 memiliki 45 sub-wabah, terhitung 722 kasus).

Meja2: Ringkasan statistik laporan penyakit kulit kental (LSD) (N=866) dari Tailand, Malaysia, Kamboja, Vietnam, Laos, dan Myanmar ke Organisasi Dunia untuk Kesehatan Hewan (WOAH) Sistem Informasi Kesehatan Hewan Dunia (WAHIS) dari 1 Oktober 2020 hingga 1 Oktober 2021.

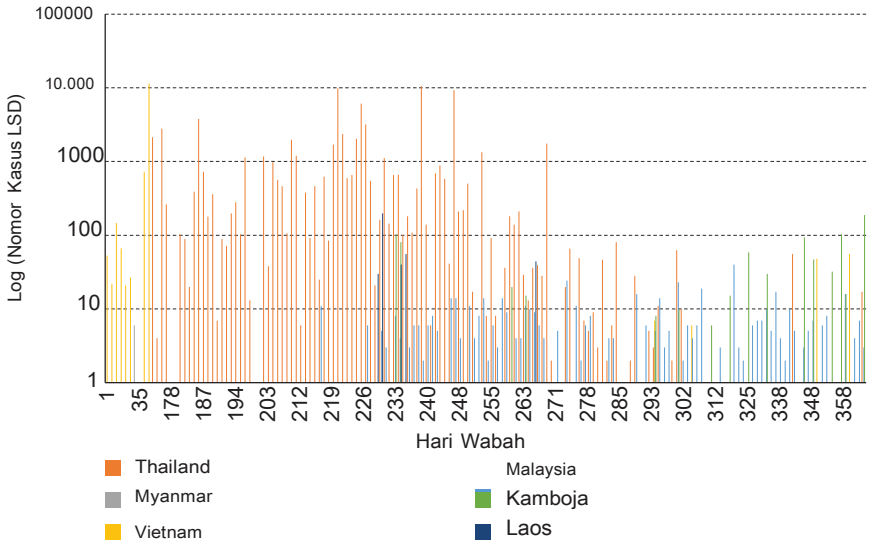
Parameter	Thailand	Malaysia	Kamboja	Vietnam	Laos	Myanmar	Rata-rata
Jumlah laporan	553	267	21	15	9	1	144.33
Hari epidemi minimum	1	1	1	1	1	1	1
1stkuartil	221	253	300	12	230	35	175.17
Berarti	234.4	286.5	321	103.5	235.3	35	205.62
median	227	275	332	22	230	35	186.83
3rdkuartil	249	325	355	183.5	234	35	230.25
Hari epidemi maksimum	205	145	127	358	31	1	144.5
IQR	28	72	55	171.5	4	0	55.08

Hari 1 ditetapkan sebagai tanggal dimulainya epidemi setiap kelompok. Rata-rata dihitung dan dilaporkan di semua negara (N=6). Data diambil dari WOAH WAHIS (https://wahis.woah.org/#/home).

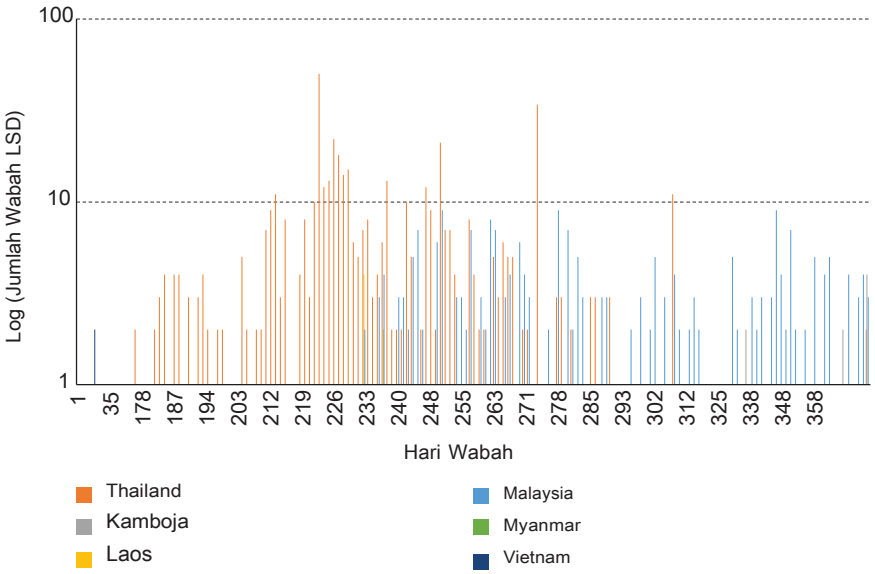
Meja3: Ringkasan statistik kasus penyakit kulit menggumpal (LSD) di Tailand, Malaysia, Kamboja, Vietnam, Laos, dan Myanmar, dilaporkan ke World Organization for Animal Health (WOAH) World Animal Health Information System (WAHIS) dari 1 Oktober 2020 hingga 1 Oktober 2021.

Parameter	Thailand	Malaysia	Kamboja	Vietnam	Laos	Myanmar	Rata-rata
Jumlah sapi rentan Jumlah	1738566	11271	3907	3098	2018	63	293153.83
kasus	78968	595	824	12703	369	6	15577.5
Kasus minimum dalam laporan	0	1	6	1	19	6	5.5
tunggal 1stkuartil	3	1	15	7.5	28	6	10.08
Berarti	147.60	2.23	39.24	846.87	41	6	180.49
median	13	1	25	27	42	6	19
3rdkuartil	74	2	70	58.5	51	6	43.58
Kasus maksimum dalam satu laporan	10317	17	103	11520	78	6	3673.5
IQR	71	1	55	51	23	0	33.5

Jumlah hewan rentan (N=1758923) dan jumlah kasus (N=93465) dilaporkan untuk setiap negara. Rata-rata dihitung dan dilaporkan di semua negara (N=6). Data diambil dari WOAH WAHIS (https://wahis.woah.org/#/home).



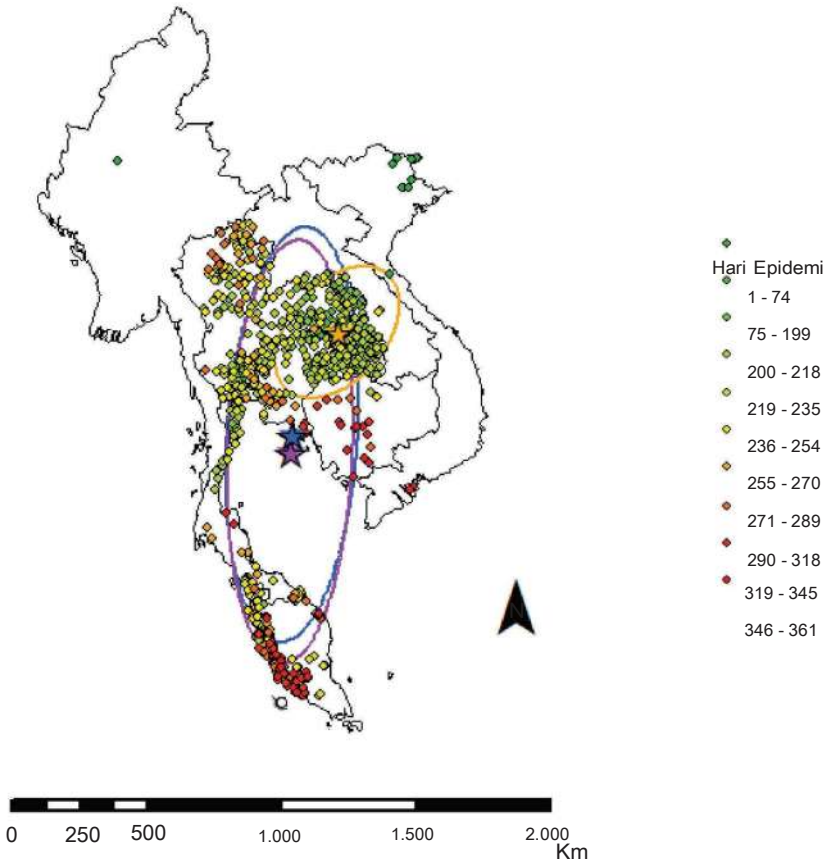
Angka1: Jumlah kasus penyakit kulit menggumpal (LSD) (skala log) yang dilaporkan dari Taiwan, Malaysia, Kamboja, Vietnam, Laos dan Myanmar ke Organisasi Dunia untuk Kesehatan Hewan (WOAH) Sistem Informasi Kesehatan Hewan Dunia (WAHIS; https://wahis .woah.org/ # /home) dari 1 Oktober 2020 hingga 1 Oktober 2021.



Angka2: Jumlah laporan penyakit kulit menggumpal (LSD) (skala log) dari Taiwan, Malaysia, Kamboja, Vietnam, Laos, dan Myanmar ke Organisasi Dunia untuk Kesehatan Hewan (WOAH) Sistem Informasi Kesehatan Hewan Dunia (WAHIS; https://wahis .woah.org/#/rumah) dari 1 Oktober 2020 hingga 1 Oktober 2021.

descriptive statistics, epidemic curves, disease mapping, and cluster analysis. Compared to what is reported in the literature, we estimated high morbidity and mortality rates in Southeast Asia and identifed Tailand as the epicentre of this regional epidemic.

Te data analysed in this investigation were limited to what was accessible and reported from each country to the WOAH WAHIS database, presenting a key limitation to this study. As this investigation relied solely on each country reporting information about their LSD outbreaks, there is potential for reporting bias. Countries with frequent reporting likely provided a more accurate description of their epidemic, whereas countries with infrequent reporting, a lack of resources, poor surveillance of LSD cases, and difering policies contribute to the lack of data accuracy. Whilst reporting should be standardised and therefore equivalent across countries, there is no guarantee that this will occur. However, the analysis of reported cases provided some important insights into the spread of LSDV in Southeast Asia during the initial incursion phase. Considering the very large number of cases reported to the WOAH WAHIS database and that LSD

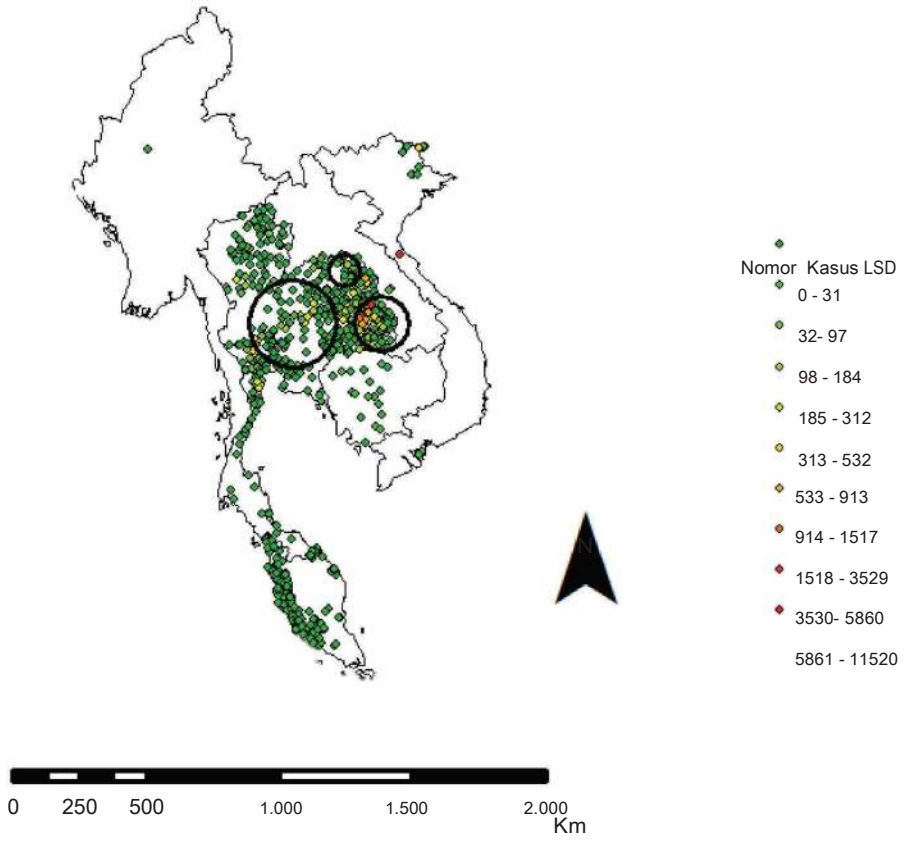


Angka3: Distribusi lokasi wabah penyakit kulit menggumpal di Asia Tenggara antara 1 Oktober 2020 dan 1 Oktober 2021. Lokasi bernaung hijau hingga merah pada hari epidemi (1–361). Hari 1 5 Oktober 2020; hari 361 1 Oktober 2021. Elips arah (1 SD) dihamparkan; tidak tertimbang (biru) dan tertimbang berdasarkan kasus (oranye) dan hari epidemi (ungu). Pusat rata-rata ditunjukkan oleh bintang; tidak tertimbang (biru) dan tertimbang berdasarkan kasus (oranye) dan hari epidemi (ungu). Data diambil dari Organisasi Dunia untuk Kesehatan Hewan (https://wahis.woah.org/#/home).

adalah sindrom penyakit baru selama 2020-2021, bias yang melekat pada data surveilans tersebut tidak mungkin memengaruhi keseluruhan kesimpulan yang dibuat secara substansial. Wabah yang berbeda juga dapat dikelompokkan bersama dan dilaporkan sebagai wabah tunggal. Klaster pelaporan ini menciptakan hambatan saat menyimpulkan dinamika peternakan dan tren epidemiologi dari data, dan deteksi klaster mengidentifikasi area di mana terdapat laporan dengan tingkat serangan yang lebih tinggi dari yang diharapkan (model Poisson), daripada area dengan insiden yang lebih tinggi. Kasus yang tidak teridentifikasi di seluruh Asia Tenggara juga mungkin terjadi, dengan risiko tidak terdeteksi karena tanda klinis yang tidak kentara, kasus subklinis, atau petani yang lalai. Estimasi morbiditas dan mortalitas mungkin bergantung pada kapan wabah diselidiki dan ketepatan waktu pelaporan dan tindak lanjut laporan. Kami membuat asumsi bahwa protokol penyelidikan wabah selama periode awal epidemi LSD di Asia Tenggara secara umum konsisten, sehingga bias sistematis dapat diminimalkan. Perlu dicatat bahwa data dari wabah di Asia Tenggara disusun hingga 15 April 2022 dan oleh karena itu mungkin berbeda dari revisi saat ini terhadap data di database WOAH WAHIS. Data diperbarui sepanjang penelitian dengan revisi yang dilakukan secara berkala pada dataset.

Sebagian besar kasus LSD dilaporkan dari Thailand dan Vietnam. Sementara lebih banyak penyakit dapat dialami di negara-negara ini, kemungkinan sistem pengawasan yang lebih efektif menghasilkan lebih banyak wabah yang dilaporkan. Selama fase awal epidemi LSD di Asia Tenggara, metode pengendalian kemungkinan serupa di seluruh wilayah, wilayah di mana sistem pengelolaan ternak biasanya didasarkan pada petani kecil. Penerapan pengendalian dan pencegahan penyakit, seperti penggunaan vaksin, apabila suatu penyakit menjadi endemik akan mengakibatkan perubahan distribusi kejadian penyakit secara spatiotemporal. Meskipun lebih banyak wabah LSD dilaporkan dari Vietnam dan Tailand, penyebaran konsisten LSD secara keseluruhan melalui Asia Tenggara pada 2020-2021 menunjukkan bahwa pelaporan penyakit bervariasi di setiap negara.

Secara keseluruhan, kami memperkirakan rata-rata tingkat morbiditas kasus di Asia Tenggara, berdasarkan laporan, sebesar 20,9%, dengan rentang yang sangat besar dari 0,001 hingga 100%. Di seluruh dunia, tingkat morbiditas LSD dapat bervariasi tergantung pada berbagai faktor di dalam dan antar negara, dengan tingkat rata-rata antara 5 dan 45% yang dilaporkan [4]. Studi menyelidiki epidemi sebelumnya di Asia melaporkan tingkat morbiditas yang sama mulai dari 0,3 sampai



Angka4: Jumlah kasus penyakit kulit kental di Asia Tenggara dari 1 Oktober 2020 hingga 1 Oktober 2021. Wabah diberi warna hijau hingga merah dengan nomor kasus (0–11520). Klaster spatiotemporal primer (13 Mei hingga 30 Juni 2021; timur), sekunder (21 April hingga 5 Juli 2021; barat) dan tersier (17 April hingga 13 Mei 2021; pusat) dihamparkan, dengan jumlah kasus yang diamati hingga yang diharapkan adalah 9,57, 4,91 , dan 11,06, masing-masing. Data diambil dari Organisasi Dunia untuk Kesehatan Hewan (https://wahis.woah.org/#/home).

30% [12, 16–18]. Sebaliknya, tingkat morbiditas yang dilaporkan dari wilayah lain di dunia lebih rendah daripada penelitian ini, seperti 8,6% di Irak [19] dan 8,7% di Yunani [20]. Dalam studi ini, tingkat morbiditas tertinggi diperkirakan untuk Thailand dan Kamboja, masing-masing 37,1% dan 22,4%. Tanpa informasi lebih lanjut yang merinci sistem manajemen yang ada untuk tempat yang terkena dampak dalam penelitian ini, sulit untuk menetapkan penyebab pasti dari tingginya angka morbiditas. Literatur menunjukkan tingkat morbiditas dapat dipengaruhi oleh masalah multifaktorial mengenai kerentanan inang, lingkungan, dan patogen. Breed sapi, status imunologi inang, populasi vektor, iklim, peternakan, kondisi manajemen, dan strain LSDV adalah aspek kunci yang perlu dipertimbangkan [2]. Berkaitan dengan kondisi manajemen, studi telah menemukan operasi petani kecil dengan ternak yang lebih kecil dan sapi lebih sedikit memiliki risiko morbiditas yang lebih besar secara statistik signifikan, dibandingkan dengan operasi yang lebih intensif [5]. Dengan sistem pengelolaan petani kecil yang mendominasi di Asia Tenggara, hal ini mungkin menjelaskan perkiraan tingkat morbiditas yang lebih tinggi.

Angka kematian rata-rata di seluruh Asia Tenggara yang diperkirakan dalam penelitian ini adalah 2,7%. Perkiraan ini lebih tinggi dari angka kematian rata-rata yang dilaporkan di negara lain namun tetap kurang dari ujung atas kisaran yang diharapkan (<10%) [4]. Di negara-negara Asia lainnya, seperti India, Hong Kong, Bangladesh, dan China, tingkat kematian 0 sampai 0,9% telah dilaporkan [12, 16-18]. Di wilayah lain di dunia, the

tingkat kematian seringkali rendah, umumnya dilaporkan <3% [19, 20]. Tingkat kematian yang diselidiki dalam penelitian ini menunjukkan Vietnam memiliki yang tertinggi (7,7%), diikuti oleh Thailand (7,3%). Angka yang tinggi ini dapat disebabkan oleh berbagai alasan, termasuk kemungkinan bias pengambilan sampel. Kedua negara ini memiliki tingkat pelaporan tertinggi untuk hewan dan kasus yang rentan, membuat skala wabah yang dilaporkan jauh lebih besar daripada negara lain. Alasan lain yang mungkin untuk tingkat kematian yang tinggi termasuk zona agro-ekologi dan sistem manajemen peternakan yang terpengaruh [21], populasi ternak yang sepenuhnya naif [22], dan kurangnya akses ke vaksin. Sebuah analisis filogenetik telah menunjukkan isolat LSDV di Tailand menjadi 99,83% mirip dengan strain dari China daratan, wilayah Hong Kong, dan Vietnam dalam strain rekombinan vaksin yang berpotensi mematikan [23]. Menurut laporan yang diserahkan ke database WOAH WAHIS, Tailand mengoordinasikan respons pengendalian dan pencegahan multifaset terhadap epidemi LSD-nya. Ini termasuk pembatasan pergerakan hewan di provinsi yang terkena dampak, penurunan impor sapi, kampanye kesadaran masyarakat untuk mendukung deteksi dini, distribusi insektisida, dan penetapan zona penahanan dalam radius 50 km dari wabah [24].

Persetujuan awal vaksinasi LSD oleh Tai Food and Drug Administration, diikuti dengan rencana vaksin, memungkinkan vaksin pertama tiba di Tailand pada 29 Mei 2021, dua bulan setelah laporan kasus pertama di negara tersebut [24]. Meskipun program vaksinasi itu Ini termasuk pembatasan pergerakan hewan di provinsi yang terkena dampak, penurunan impor sapi, kampanye kesadaran masyarakat untuk mendukung deteksi dini, distribusi insektisida, dan penetapan zona penahanan dalam radius 50 km dari wabah [24]. Persetujuan awal vaksinasi LSD oleh Tai Food and Drug Administration, diikuti dengan rencana vaksin, memungkinkan vaksin pertama tiba di Tailand pada 29 Mei 2021, dua bulan setelah laporan kasus pertama di negara tersebut [24]. Meskipun program vaksinasi itu Ini termasuk pembatasan pergerakan hewan di provinsi yang terkena dampak, penurunan impor sapi, kampanye kesadaran masyarakat untuk mendukung deteksi dini, distribusi insektisida, dan penetapan zona penahanan dalam radius 50 km dari wabah [24]. Persetujuan awal vaksinasi LSD oleh Tai Food and Drug Administration, diikuti dengan rencana vaksin, memungkinkan vaksin pertama tiba di Tailand pada 29 Mei 2021, dua bulan setelah laporan kasus pertama di negara tersebut [24]. Meskipun program vaksinasi itu memungkinkan vaksin pertama tiba di Tailand pada 29 Mei 2021, dua bulan setelah laporan kasus pertama di negara tersebut [24]. Meskipun program vaksinasi itu memungkinkan vaksin pertama tiba di Tailand pada 29 Mei 2021, dua bulan setelah laporan kasus pertama di negara tersebut [24]. Meskipun program vaksinasi itu

segera dimulai, penyebaran LSDV sudah terjadi sebelum implementasi. Tidak jelas bagaimana jadwal vaksinasi dilaksanakan atau apakah semua wilayah di Tailand memiliki akses, sumber daya yang memadai, dan pendidikan untuk memvaksinasi sapi mereka dengan tepat. Peran vaksinasi di Asia Tenggara membutuhkan investigasi.

5. Kesimpulan

Investigasi ini menemukan LSD di Asia Tenggara memiliki tingkat morbiditas dan mortalitas yang tinggi secara umum dalam epidemi yang terjadi antara 1 Oktober 2020 dan 1 Oktober 2021. Kurangnya program vaksin yang efektif dan kenaifan populasi sapi di Asia Tenggara kemungkinan besar berkontribusi pada tingginya angka kematian ini. perkiraan; namun, penelitian lebih lanjut tentang faktor risiko spesifik yang memengaruhi angka morbiditas dan mortalitas di Asia Tenggara diperlukan. Sementara wabah dilaporkan dari enam negara Asia Tenggara, Tailand diidentifikasi sebagai episentrum epidemi regional ini selama periode penelitian. Kelimpahan vektor, virulensi strain dan penularan, manajemen, kontrol, dan faktor pencegahan kemungkinan berkontribusi pada dominasi di wilayah ini. Untuk membantu mengurangi penyebaran penyakit lebih lanjut, khususnya ke kawasan Asia-Pasifik dan Oseania,

Ketersediaan Data

Data tersedia melalui Sistem Informasi Kesehatan Hewan Dunia, https://wahis.woah.org/#/home.

Konflik kepentingan

Para penulis menyatakan bahwa tidak ada konflik kepentingan.

Terima kasih

Penulis mengakui Organisasi Dunia untuk Kesehatan Hewan (WOAH) karena menyediakan akses gratis ke data yang digunakan untuk penelitian ini. Pekerjaan ini diselesaikan untuk memenuhi sebagian persyaratan gelar Doctor of Veterinary Medicine, Te University of Sydney, dan didanai oleh Sydney School of Veterinary Science.

Bahan Pelengkap

Gambar tambahan A: jumlah kasus penyakit kulit menggumpal (LSD) (skala log) yang dilaporkan dari masing-masing Thailand, Malaysia, Kamboja, Vietnam, Laos, dan Myanmar ke Sistem Informasi Kesehatan Hewan Dunia Organisasi Dunia untuk Kesehatan Hewan (WOAH) (WAHIS) ; https://wahis.woah.org/#/ home), 1 Oktober 2020 hingga 1 Oktober 2021. Gambar tambahan B: jumlah wabah penyakit kulit menggumpal (LSD) (skala log) yang dilaporkan dari masing-masing Tailand, Malaysia, Kamboja , Vietnam, Laos, dan Myanmar kepada World Organization for Animal Health (WOAH) World Animal Health Information System (WAHIS; https://wahis.woah.org/#/home), mulai 1 Oktober 2020 hingga 1 Oktober 2021. (Bahan Pelengkap)

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MDPI

Artikel

Wabah *Lumpy Skin Disease* di Afrika, Eropa, dan Asia (2005–2022): Analisis Titik Perubahan Berganda dan Ramalan Deret Waktu

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Abstrak: LSD adalah penyakit lintas batas penting yang mempengaruhi industri peternakan di seluruh dunia. Tujuan dari penelitian ini adalah untuk menentukan tren dan titik perubahan yang signifikan, dan untuk meramalkan jumlah laporan wabah LSD di Afrika, Eropa, dan Asia. Data laporan wabah LSD (Januari 2005 hingga Januari 2022) dari Organisasi Kesehatan Hewan Dunia dianalisis. Kami menentukan titik perubahan yang signifikan secara statistik dalam data menggunakan segmentasi biner, dan memperkirakan jumlah laporan LSD menggunakan model auto-regressive moving average (ARIMA) dan neural network auto-regressive (NNAR). Empat titik perubahan signifikan telah diidentifikasi untuk setiap benua. Tahun antara titik perubahan ketiga dan keempat (2016–2019) dalam data Afrika adalah periode dengan rata-rata jumlah laporan LSD tertinggi. Semua titik perubahan wabah LSD di Eropa berhubungan dengan wabah masif selama 2015-2017. Asia memiliki jumlah laporan LSD tertinggi pada tahun 2019 setelah titik perubahan ketiga terdeteksi pada tahun 2018. Selama tiga tahun ke depan (2022–2024), ARIMA dan NNAR memperkirakan peningkatan jumlah laporan LSD di Afrika dan jumlah yang stabil di Eropa. Namun, ARIMA memperkirakan jumlah wabah yang stabil di Asia, sedangkan NNAR memperkirakan peningkatan pada tahun 2023–2024. Studi ini memberikan informasi yang memberikan kontribusi untuk pemahaman yang lebih baik tentang epidemiologi LSD. ARIMA memperkirakan jumlah wabah yang stabil di Asia, sedangkan NNAR memperkirakan peningkatan pada tahun 2023–2024. Studi ini memberikan informasi yang memberikan kontribusi untuk pemahaman yang lebih baik tentang epidemiologi LSD. ARIMA memperkirakan jumlah wabah yang stabil di Asia, sedangkan NNAR memperkirakan peningkatan pada tahun 2023–2024. Studi ini memberikan informasi yang memberikan kontribusi untuk pemahaman yang lebih baik tentang epidemiologi LSD.

Kata kunci: penyakit kulit kental; analisis titik perubahan; deret waktu; wabah; ramalan; Afrika; Eropa; Asia

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Catatan Penerbit: MDPI tetap netral sehubungan dengan klaim yurisdiksi dalam peta yang diterbitkan dan afiliasi kelembagaan.

1. Perkenalan

Lumpy Skin Disease (LSD) adalah penyakit virus lintas batas yang muncul yang disebabkan oleh virus *Lumpy Skin Disease* (LSDV), yang termasuk dalam Capripoxvirus genus dari poxviridae keluarga [1]. Sapi dan kerbau adalah inang utama dari penyakit ini [2], tetapi beberapa hewan liar, seperti jerapah, springboks, dan kijang, juga dapat terinfeksi [3]. Vektor Arthropoda, seperti kutu, lalat penggigit, dan nyamuk, adalah pembawa mekanik dari LSDV [4–7]. Tanda-tanda klinis pada hewan yang sakit adalah demam, lakrimasi, nodul kulit, sekret hidung, edema kulit, dan pembesaran kelenjar getah bening.8,9]. Ini juga dapat menyebabkan produksi susu berkurang dan dapat menyebabkan kematian. LSD cenderung memiliki morbiditas hingga 90% dan mortalitas kurang dari 10% [10]. Organisasi Dunia untuk Kesehatan Hewan (WOAH) telah menempatkan LSD pada daftar penyakit yang harus dilaporkan [11].

Pada tahun 1929, wabah pertama LSD terjadi di Zambia, dan dalam dekade berikutnya, virus menyebar ke sub-Sahara Afrika.12]. LSD dilaporkan di luar Afrika (di Mesir) untuk pertama kalinya pada tahun 1989 [13]. Sejak itu, wabah LSD berulang telah dilaporkan di Timur Tengah [14]. Dari tahun 2012 hingga 2014, penyakit ini menyebar di Lebanon, Turki, Israel, Irak, Yordania, Iran, Azerbaijan, dan Siprus [15]. Dari 2014 hingga 2015, penyakit ini menyebar dari Asia ke Eropa [16]. Kemudian, pada tahun 2015, penyakit ini semakin menyebar di negara-negara Eropa, antara lain Yunani, Rusia, Armenia, Azerbaijan, Albania, Bulgaria, Serbia, Montenegro, dan Kosovo.14,16–19]. Pada tahun 2016, banyak wabah LSD ditemukan di Eropa Tenggara. Selama 2019 hingga 2020, penyakit ini menjadi lazim di banyak negara di Asia [20–25]. Saat ini, penyakit tersebut dianggap sebagai ancaman besar bagi industri ternak dan mata pencaharian peternak sapi di banyak wilayah di Asia. Karena wabah LSD terus dilaporkan di berbagai benua dengan pola yang berbeda- beda, mengidentifikasi tren dan titik perubahan dalam tren tersebut akan meningkatkan pemahaman kita tentang epidemiologi penyakit ini.

Analisis titik perubahan dan analisis tren adalah metode statistik yang umumnya digunakan untuk menentukan dan memantau perilaku data deret waktu [26]. Istilah "titik perubahan" menggambarkan waktu di mana perubahan mulai terjadi. Analisis titik perubahan dapat mendeteksi perubahan mendadak atau struktural dalam data deret waktu. Misalnya, jumlah laporan wabah LSD yang dikumpulkan dari negara yang sama selama periode tertentu (mis., setiap bulan selama bertahun-tahun) dianggap sebagai data deret waktu. Memang, jumlah laporan wabah LSD mungkin konstan, berubah, atau berfluktuasi dari tahun ke tahun atau periode ke periode (misalnya, setiap 2-3 tahun). Oleh karena itu, perubahan kecil pada data deret waktu mungkin tidak terlalu menarik; namun, perubahan besar atau mendadak perlu diselidiki. Beberapa penelitian telah menunjukkan kegunaan analisis titik perubahan dalam mendeteksi titik perubahan COVID-19 [26–28] dan malaria [29].

Beberapa publikasi penelitian telah memberikan informasi penting tentang status global dan situasi regional atau negara dari wabah LSD. Misalnya penyebaran LSD dari Afrika ke Eropa, Timur Tengah, dan Asia.30]; epidemiologi LSD di Asia dan negara-negara Asia Tenggara [31]; dan situasi di daerah tertentu [32] dan negara-negara, seperti India [33] dan Bangladesh [34], semuanya telah dijelaskan. Namun, hanya beberapa laporan sebelumnya yang menggambarkan tren deret waktu kejadian LSD, dan tidak satu pun dari mereka yang menyelidiki perubahan signifikan dalam jumlah laporan menggunakan metode deteksi titik perubahan deret waktu. Selain itu, studi tentang peramalan jumlah laporan LSD menggunakan model deret waktu sangat terbatas.

Peramalan penyakit menggunakan metode prediksi yang diterima dengan baik sangat penting untuk mengembangkan rencana strategis untuk memantau dan mencegah wabah penyakit. Prediksi COVID-19, yang muncul dalam ratusan publikasi, adalah contoh utama penerapan metodologi peramalan secara luas [35,36]. Prakiraan penyakit hewan menular juga ditunjukkan dalam berbagai penelitian [37,38]. Ada beberapa teknik peramalan berdasarkan kerangka kerja statistik dan alat berbasis data. Dalam penelitian ini, kami menggunakan model auto-regressive moving average (ARIMA) dan neural network auto-regressive (NNAR). ARIMA adalah model statistik klasik umum, sedangkan NNAR adalah metode yang didasarkan pada pembelajaran mesin. Pendekatan ini banyak digunakan di berbagai disiplin ilmu. Meskipun berbagai metode deret waktu tersedia, ruang lingkup penelitian ini difokuskan pada ARIMA dan NNAR.

Secara sistematis, laporan wabah LSD dari berbagai wilayah di dunia telah dipublikasikan secara terus menerus oleh WOAH. Untuk pemahaman yang lebih baik tentang epidemiologi LSD, tren, titik perubahan tren penyakit, dan prakiraan wabah LSD perlu diselidiki. Dengan demikian, tujuan penelitian ini adalah: (i) menentukan tren dan titik perubahan pada data deret waktu, dan (ii) meramalkan jumlah laporan LSD berdasarkan data dari Afrika, Eropa, dan Asia.

2. Bahan-bahan dan metode-metode

2.1. Data Wabah LSD

Dalam penelitian ini, data jumlah laporan LSD di Afrika, Eropa, dan Asia dari Januari 2005 hingga Januari 2022, tersedia untuk umum di situs web resmi WOAH (https://wahis.woah.org, diakses pada 14 Agustus 2020), diimpor dan dianalisis. Berdasarkan file laporan WOAH, jumlah laporan LSD ditampilkan sebagai data dua tahunan. Misalnya, tahun 2020 memiliki dua semester, semester pertama mencakup total laporan LSD dari Januari hingga Juni 2020, dan semester kedua mencakup Juli hingga Desember 2020.

2.2. Ubah Analisis Titik

Analisis titik perubahan diterapkan pada data untuk menentukan perubahan signifikan dalam jumlah laporan LSD dari waktu ke waktu. Pendekatan deteksi titik perubahan berbasis kemungkinan digunakan untuk mendeteksi perubahan rata-rata dan varians dari jumlah laporan LSD. Karena jumlah laporan LSD merupakan data hitung, maka diasumsikan mengikuti distribusi Poisson.

Itucpt.meanvarfungsi dari paket titik perubahan mendeteksi perubahan rata-rata dan varians untuk empat jenis distribusi data: eksponensial, gamma, Poisson, dan normal. Salah satu keuntungan utama dari fungsi ini adalah kemampuannya untuk mendeteksi banyak titik perubahan [39]. Penggunaan fungsi ini telah dibuktikan dalam beberapa penelitian. Teknik segmentasi biner dicpt.meanvardipekerjakan.

Teknik segmentasi biner memperkirakan perkiraan minimum Persamaan (1). Itucpt.meanvar algoritma pertama-tama mendeteksi satu titik perubahan dalam kumpulan data. Setelah menentukan titik perubahan pertama, data dibagi menjadi 2 subsegmen di lokasi titik perubahan. Proses titik perubahan tunggal diulang pada 2 dataset. Jika titik perubahan lebih lanjut terdeteksi, data kemudian dibagi menjadi subsegmen lebih lanjut. Prosedur ini diulang sampai tidak ada titik perubahan yang ditemukan di subsegmen [26,39].

Mengingat m segmen data deret waktu, deteksi titik perubahan berdasarkan teknik ini dicapai dengan meminimalkan fungsi [39]:

$$\sum_{\text{Saya}=1}^{M+1} C\left(\quad_{(TSaya-1):TSaya}\right) + \beta f(m) \qquad (1)$$

Di mana**C**adalah biaya dalam fungsi untuk segmen, dan**βF(M)**adalah hukuman untuk mencegah overfitting.

2.3. Peramalan Wabah LSD

Model ARIMA dan NNAR digunakan untuk memprediksi jumlah laporan LSD selama 3 tahun ke depan (2022–2024) untuk setiap benua. Teknik ARIMA didasarkan pada prinsip bahwa nilai masa depan dari deret waktu dihasilkan dari fungsi linear dari pengamatan masa lalu dan suku white noise [40]. Model ARIMA dinyatakan dengan persamaan berikut [41]:

$$y_T = \alpha + \varphi_1 y_{T-1} + \varphi_2 y_{T-2} + \cdots + \varphi_P y_{T-P} + \varepsilon_T - \theta_1 \varepsilon_{T-1} - \theta_2 \varepsilon_{T-2} - \cdots - \theta_Q \varepsilon_{T-Q} \qquad (2)$$

Di mana$y_T$menunjukkan nilai yang diamati pada waktu**T**;αadalah konstanta;$\varphi_1, \varphi_2, \ldots, \varphi_PDan\theta_1, \theta_2, \ldots, \theta_Q$ masing-masing mewakili parameter autoregressive dan moving average; Dan$\varepsilon_T$adalah nilai residu pada saat itu**T**.

ARIMA memiliki tiga parameter yang dapat ditulis sebagai ARIMA (**P**,**D**,**Q**), Di mana**P**,**D**, Dan**Q**mewakili urutan autokorelasi, urutan perbedaan, dan urutan rata-rata bergerak, masing-masing [42].

Model NNAR menggunakan nilai lagged dari data deret waktu sebagai input ke jaringan saraf. Untuk data non-musiman, ia memiliki notasi NNAR (**P**,**k**), dengan**P**Dan**k**menunjukkan input dan node yang tertinggal, masing-masing, di lapisan tersembunyi [42]. Salah satu perbedaan utama antara ARIMA dan NNAR adalah model NNAR tidak memerlukan nilai stasioner untuk peramalan [43].

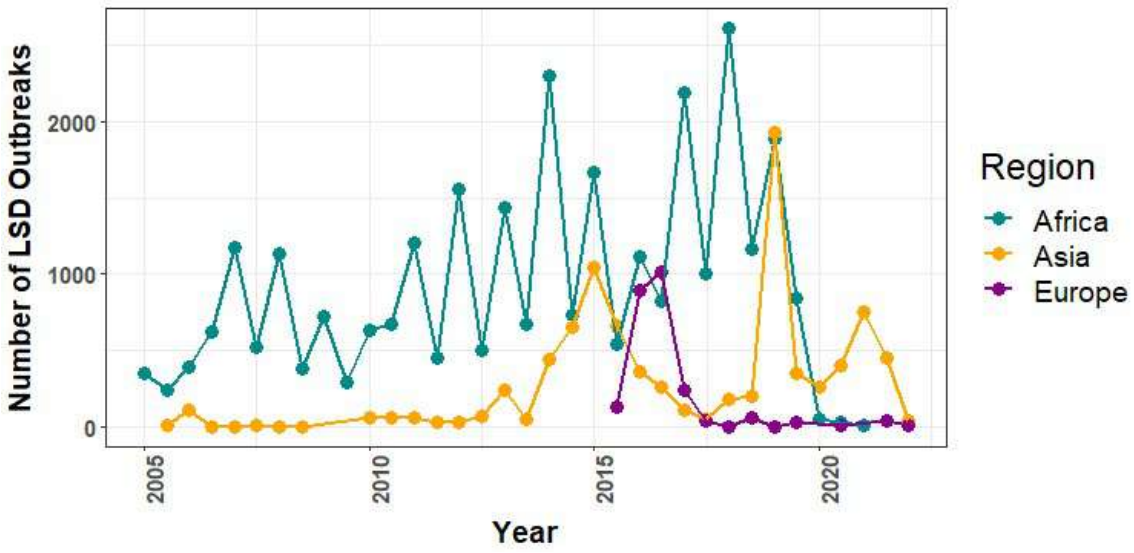
Peramalan laporan wabah LSD dilakukan dengan menggunakan perangkat lunak statistik R dan paket "dplyr", "xts", "tsbox", "TSstudio", dan "forecast". Ituauto.arimafungsi melakukan 3 langkah secara otomatis: (i) pembedaan data hingga data menjadi stasioner, (ii) memeriksa ACF dan PACF untuk data yang dibedakan dan memilih model kandidat potensial, dan (iii) membandingkan model yang dipilih menggunakan kriteria informasi Akaike (AIC) [42, 44]. Secara teknis, hasil dari semua model kandidat dengan AIC-nya dihasilkan. Model dengan AIC terendah kemudian dianggap sebagai model yang paling cocok (model final). Demikian pula,nnarfungsi, algoritme otomatis dalam paket prakiraan, menyediakan prosedur untuk menentukan model NNAR yang paling pas sebagai keluaran [42].

Selain itu, data Afrika dibagi menjadi dua set data: satu mencakup tahun 2005–2015 (set pelatihan) dan satu lagi mencakup tahun 2016–2020 (set validasi). Set pelatihan digunakan untuk membangun model ARIMA dan NNAR, keduanya digunakan untuk menghasilkan nilai ramalan. Selanjutnya, nilai yang diperkirakan dibandingkan dengan yang sebenarnya di set validasi. Selain itu, metrik kesalahan, termasuk kesalahan persentase absolut rata-rata (MAPE), kesalahan skala absolut rata-rata (MASE), dan root mean square error (RMSE), dihitung menggunakan fungsi dari paket "Metrik" untuk mengukur kemampuan prediksi dari model ARIMA dan NNAR [42,45].

3. Hasil

3.1. Laporan Wabah *Lumpy Skin Disease*

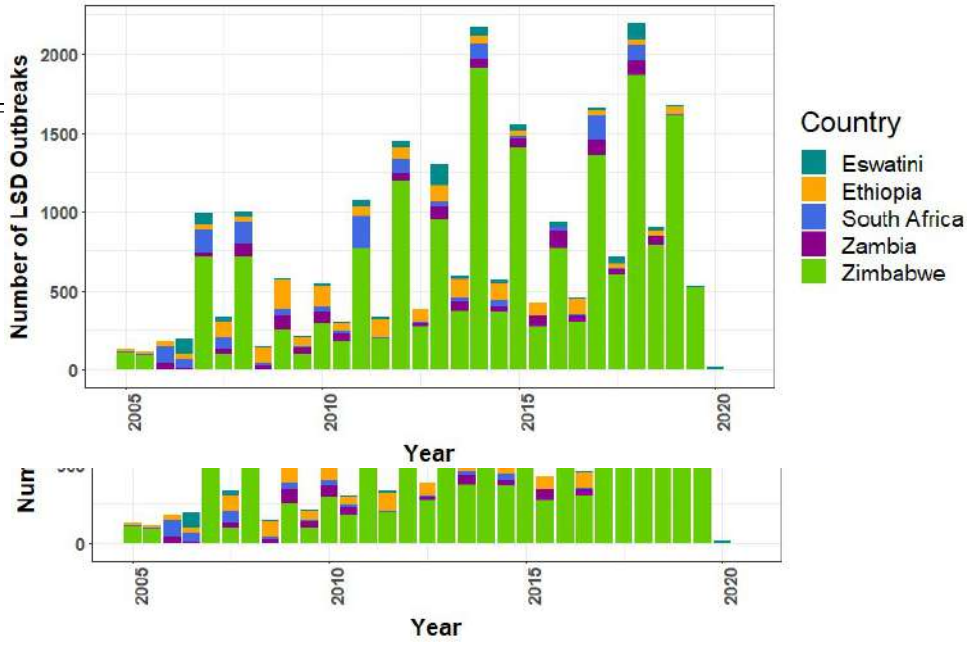
Secara keseluruhan, Afrika memiliki 29.966, Asia memiliki 8.837, dan Eropa memiliki 2.471 laporan wabah selama periode penelitian. Afrika memiliki tren bergelombang selama 2005–2019, dan pada akhir tahun 2020, wabah telah turun tajam dan tetap rendah secara konsisten, sedangkan Eropa mencapai puncaknya pada tahun 2016, penurunan tajam pada tahun 2017, dan kemudian menjadi stabil, dan Asia memiliki tiga puncak. sepanjang periode (Gambar1).



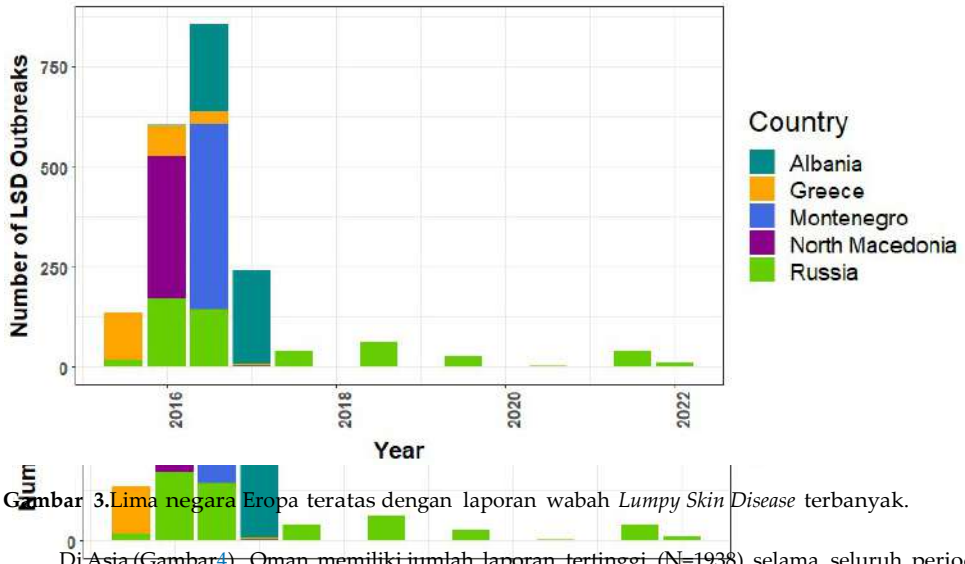
Gambar 1. Tren keseluruhan wabah LSD di Afrika, Asia, dan Eropa dari tahun 2005 hingga 2020.

Mengenai lima negara Afrika teratas yang melaporkan wabah LSD terbanyak (Gambar2), Zimbabwe secara konsisten mencatat wabah dari tahun 2005 hingga 2019, kecuali tahun 2006. Dibandingkan dengan negara lain, Zimbabwe memiliki wabah yang paling banyak tercatat (N=18.072), dengan jumlah terbanyak terjadi pada tahun 2014 (N=1915). Ethiopia, peringkat kedua, telah melaporkan wabah selama beberapa tahun.

Di Eropa, Rusia memiliki jumlah wabah LSD tertinggi (N=524), diamati pada tahun 2016. Makedonia Utara, Albania, Montenegro, Rusia, dan Yunani adalah lima negara Eropa teratas yang melaporkan wabah LSD tahun itu (Gambar3). Setelah puncaknya pada tahun 2016, jumlah laporan menurun tajam. Dari 2018 hingga 2020, Rusia melaporkan wabah LSD setiap tahun.

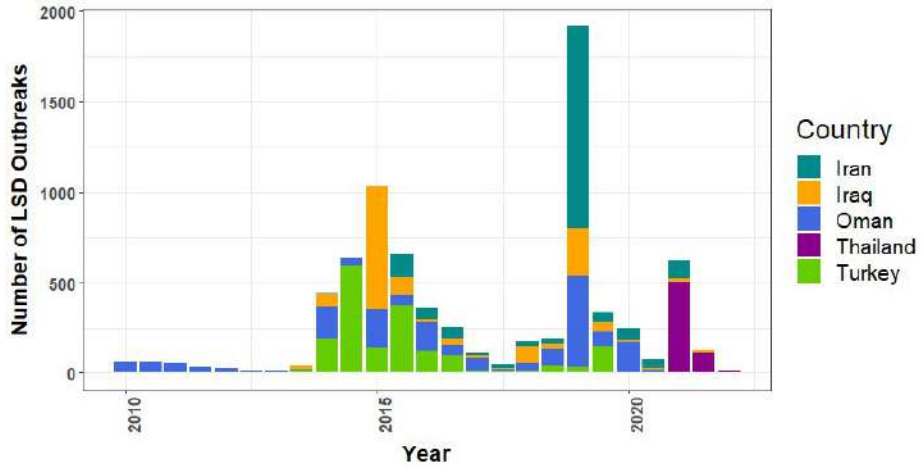


Gambar 2. Lima negara Afrika teratas dengan laporan wabah *Lumpy Skin Disease* terbanyak.



Gambar 3. Lima negara Eropa teratas dengan laporan wabah *Lumpy Skin Disease* terbanyak.

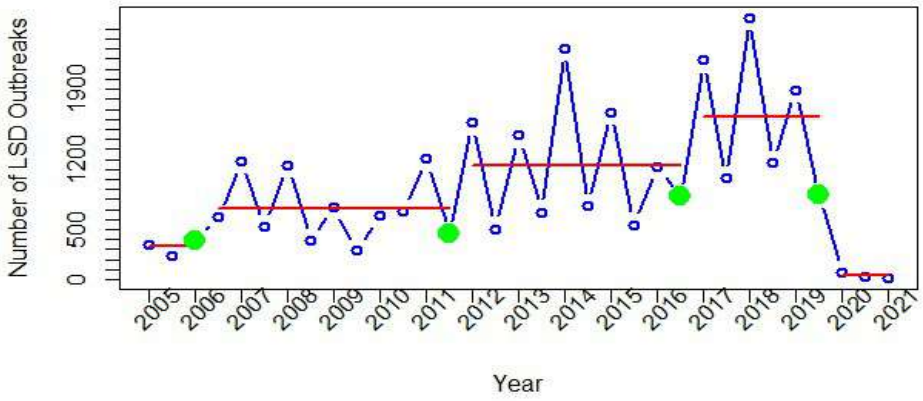
Di Asia (Gambar 4), Oman memiliki jumlah laporan tertinggi (N=1938) selama seluruh periode penelitian, dengan maksimum pada tahun 2019. Dari tahun 2013 hingga 2019, Turki melaporkan jumlah epidemi LSD yang sangat tinggi pada tahun 2014 dan 2015. Iran memiliki jumlah tertinggi pada tahun 2019. Selama periode dari tahun 2021 hingga Januari 2022, Thailand memiliki jumlah laporan LSD tertinggi.



Gambar 4. Lima negara Asia teratas dengan laporan wabah *Lumpy Skin Disease* terbanyak. Khususnya, berdasarkan data World Organization for Animal Health (WOAH), Turki dikategorikan sebagai bagian dari Asia.

3.2. Perubahan Poin pada Data Time Series Laporan Wabah Penyakit Kulit Bergumpal

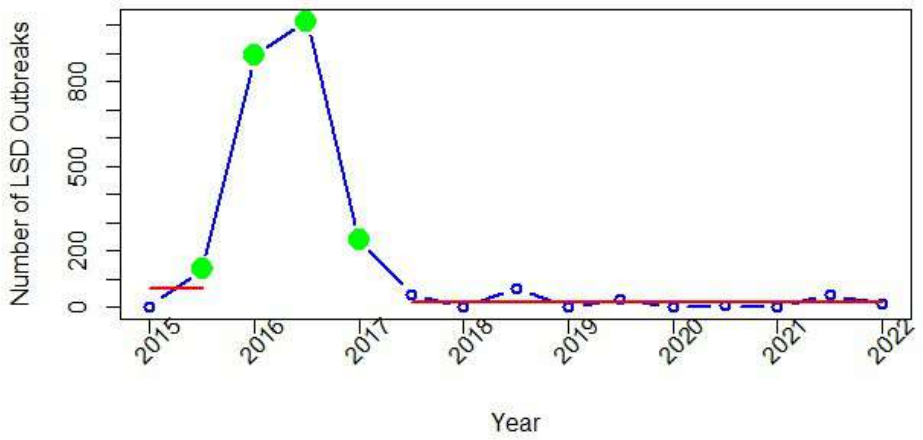
Data deret waktu dari jumlah laporan LSD memiliki empat titik perubahan untuk setiap benua. Secara teknis, setelah titik perubahan diidentifikasi, segmen yang c di fi berarti Hai ment.



Gambar 5. Ubah poin dalam rangkaian waktu laporan wabah LSD di Afrika. Titik hijau adalah titik perubahan, dan garis merah adalah segmen yang sesuai.

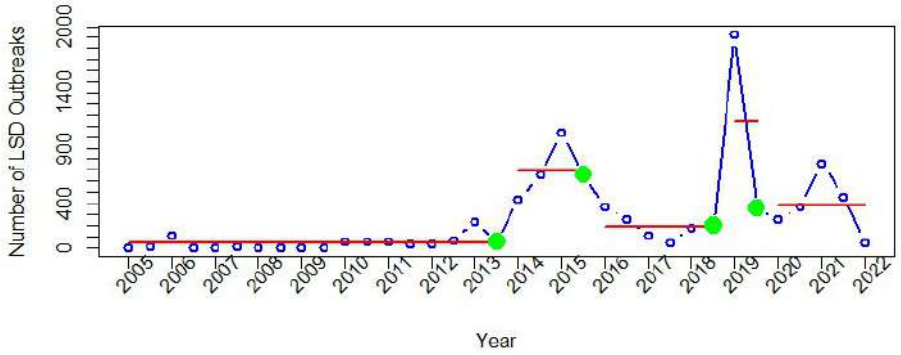
Diamati bahwa segmen keempat dari data Afrika (Gambar5) memiliki rata-rata jumlah laporan LSD tertinggi dibandingkan dengan segmen lainnya. Segmen keempat menyoroti jumlah laporan yang sangat tinggi selama 2017–2019. Menyusul titik perubahan keempat, jumlah laporan LSD turun tajam, dan tetap stabil sejak 2020.

Untuk Eropa, keempat titik perubahan terdeteksi selama 2015–2017 (Gambar6). Titik perubahan pertama teridentifikasi pada semester kedua tahun 2015. Titik perubahan kedua terdeteksi pada tahun 2016, dimana terjadi peningkatan jumlah laporan LSD yang signifikan dibandingkan dengan saat perubahan titik pertama. Dari poin perubahan ketiga ke keempat, a terdeteksi C e sejak T



Gambar 6. Ubah poin dalam deret waktu laporan wabah LSD di Eropa. Titik hijau adalah titik perubahan, dan garis merah adalah segmen yang sesuai.

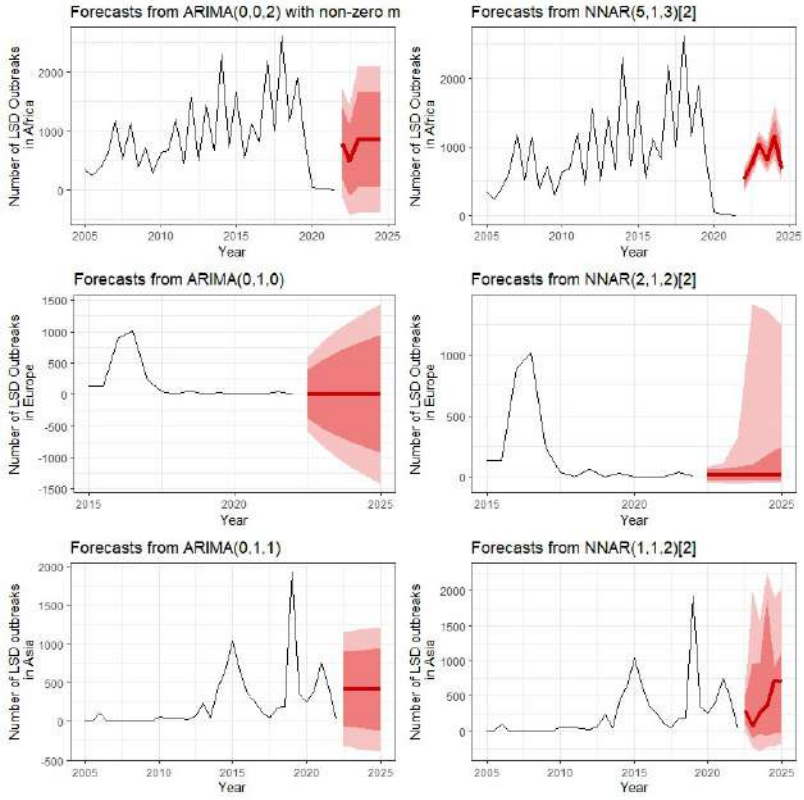
Untuk Asia, empat titik perubahan dan lima segmen yang sesuai dengannya diidentifikasi (Gambar7). Segmen pertama, dari tahun 2005 hingga 2013, menunjukkan pola yang konsisten dengan jumlah laporan wabah yang rendah. Setelah titik perubahan ketiga terdeteksi pada semester kedua 2012, jumlah laporan wabah LSD tertinggi diamati pada semester pertama 2019. Kemudian, titik perubahan keempat diidentifikasi pada semester kedua 2019.



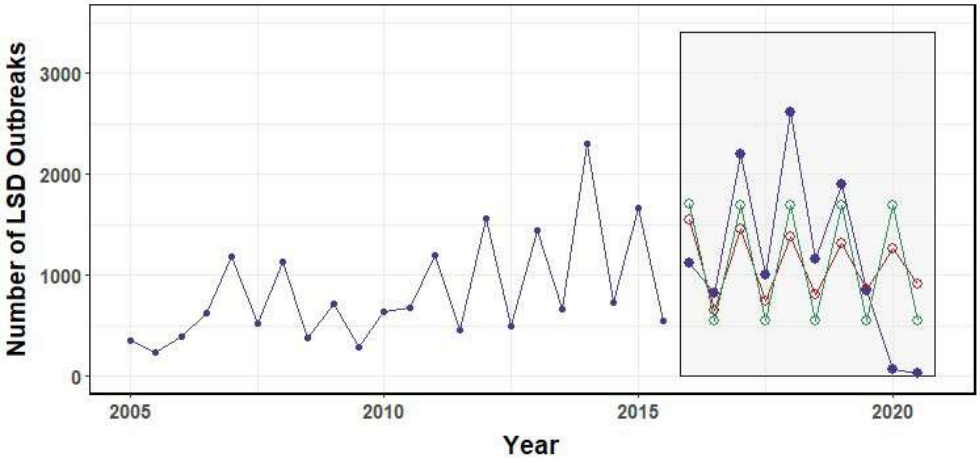
Gambar 7. Ubah poin dalam rangkaian waktu laporan wabah LSD di Asia. Titik hijau adalah titik perubahan, dan garis merah adalah segmen yang sesuai.

3.3. Prakiraan Wabah LSD

Peramalan wabah LSD di Afrika, Eropa, dan Asia oleh ARIMA dan NNAR ditunjukkan pada Gambar8. Untuk Afrika, baik ARIMA maupun NNAR memprediksi tren wabah LSD yang meningkat, sedangkan untuk Eropa, kedua model memprediksi bahwa wabah akan stabil. Namun, di Asia, ARIMA memprediksikan jumlah wabah yang stabil, sedangkan NNAR memprediksikan wabah yang berfluktuasi, yang kira-kira mirip dengan pola sebelumnya. Model yang paling cocok di ARIMA (**P**,**D**,**Q**) dan NNAR (**P**,**k**) notasi yang diperoleh dari analisis ditunjukkan pada Gambar8. Selain itu, hasil menunjukkan bahwa beberapa nilai ramalan NNAR lebih mendekati nilai sebenarnya daripada nilai ramalan ARIMA; namun demikian, beberapa nilai ramalan ARIMA lebih dekat dengan nilai sebenarnya daripada nilai ramalan NNAR (Gambar9). Selain itu, model NNAR menghasilkan nilai MAPE, MASE, dan RMSE masing-masing sebesar 4,48, 0,6, dan 730,97, sedangkan model ARIMA masing-masing menghasilkan 4,77, 0,63, dan 726,94. Temuan ini menunjukkan bahwa kinerja prediksi dari kedua model kira-kira sebanding.



Angka 8. Jumlah wabah LSD di Afrika, Eropa, dan Asia yang diramalkan oleh ARIMA dan NNAR. Garis tengah tebal mewakili prakiraan titik laporan wabah LSD; nuansa gelap dan terang masing-masing menunjukkan interval kepercayaan 95% dan 80%.



Gambar 9. Laporan wabah LSD di Afrika. Model perkiraan dibuat dengan data dari tahun 2005 hingga 2015, dan divalidasi dengan data dari tahun 2016 hingga 2022. Kotak abu-abu mewakili perbandingan antara perkiraan nilai wabah LSD yang diperoleh oleh model ARIMA (lingkaran merah) dan NNAR (lingkaran hijau) dan nilai wabah aktual (titik biru).

4. Diskusi

Poin perubahan dalam data deret waktu wabah LSD memberikan informasi kapan perubahan signifikan terjadi pada data, yang merupakan informasi penting untuk epidemiologi, khususnya dalam dimensi temporal. Prakiraan jumlah laporan LSD berdasarkan metode prakiraan yang diterima dengan baik menawarkan data dasar yang berguna yang dapat membantu pihak berwenang dalam merencanakan upaya pengawasan dan pencegahan penyakit.

Setelah wabah pertama di Zambia pada tahun 1929, penyakit ini menjadi lazim di beberapa wilayah Afrika [30]. Zimbabwe memiliki jumlah laporan LSD tertinggi selama hampir seluruh periode penelitian (Gambar2). Temuan ini mungkin karena perubahan land reform yang mengacaukan distribusi ternak di Zimbabwe [46,47]. Ethiopia memiliki jumlah laporan LSD tertinggi, dengan jumlah yang stabil selama periode tersebut; semua bagian negara menderita penyakit kecuali Dire Dawa dan Harari [48]. Beberapa wabah di Ethiopia diduga terkait dengan populasi vektor, kondisi kotor di peternakan, vaksinasi yang tidak tepat [49], pergerakan ternak yang terinfeksi, dan air umum dan sistem penggembalaan [48].

Temuan kami selanjutnya menunjukkan bahwa segmen keempat (Gambar5) memiliki jumlah rata-rata laporan wabah LSD terbesar jika dibandingkan dengan periode lain yang diidentifikasi dengan analisis titik perubahan. Pada tahun itu, wabah terjadi di beberapa negara Afrika. Misalnya, sebuah penelitian di Ethiopia melaporkan upaya pengendalian untuk membatasi wabah LSD pada tahun 2017 dengan menggunakan vaksinasi. Meskipun penggunaan vaksin virus cacar domba Kenya (KS1 O-180) selama tahun itu, wabah terus terjadi. Diperkirakan bahwa vaksin KS1 O-180 mungkin kurang efisien dalam mengendalikan wabah [50]. Akibatnya, banyak wabah dilaporkan dari Ethiopia, yang terkait dengan segmen setelah titik perubahan ketiga yang disebutkan di atas. Selain itu, penelitian menunjukkan bahwa banyak wabah LSD diamati di Mesir dari tahun 2016 hingga 2018 [51,52]. Faktor risiko yang terkait dengan wabah di beberapa wilayah Mesir sebanding dengan yang terlihat di Ethiopia, termasuk sumber air bersama, kontak hewan satu sama lain, dan pengenalan hewan baru di peternakan [52]. Sangat menarik bahwa jumlah laporan wabah telah menurun drastis sejak Juli 2019 (Gambar2), tetapi, saat ini, belum ada penelitian yang dilakukan untuk menjelaskan fenomena ini dengan jelas.

Di Eropa, empat titik perubahan dan hanya dua segmen yang diidentifikasi. Poin perubahan ini sesuai dengan situasi penyakit pada tahun 2015–2016. Titik perubahan pertama ditemukan pada awal tahun 2015, ketika wabah LSD pertama terjadi di Yunani (Gambar3Dan6). Titik perubahan kedua mewakili jumlah laporan wabah LSD yang sangat tinggi. Titik perubahan kedua dan ketiga sesuai dengan periode tahun 2016 ketika laporan wabah mencapai puncak tertinggi kedua dan tertinggi. Titik perubahan ini mungkin disebabkan oleh

penyebaran penyakit di wilayah Balkan [53]. Selama periode yang sama, Turki melaporkan wabah LSD, dan dari sana penyakit ini menyebar ke Yunani. Karena cakupan vaksinasi yang lebih sedikit, penyakit ini kemudian menyebar ke Bulgaria, Serbia, Makedonia, Montenegro, dan Kosovo pada tahun 2016 [54]. Banyak wabah LSD di Eropa Timur ditemukan terkait dengan kedekatan dengan peternakan yang terkena dampak, suhu tinggi, dan banyaknya vektor terkait [16]. Kolaborasi lintas batas oleh otoritas veteriner di beberapa negara yang dikoordinasikan oleh Komisi Eropa menjadi kunci untuk menghentikan penyebaran penyakit dari tahun 2015 hingga 2017 di Eropa tenggara [53]. Tidak ada wabah yang dilaporkan di Eropa Tenggara pada tahun 2019 sebagai hasil dari program imunisasi massal di kawasan itu, dengan lebih dari 1,8 juta sapi diinokulasi dengan vaksin homolog [55]. Setelah titik perubahan keempat yang terdeteksi pada tahun 2017, dari semester kedua tahun 2017 hingga Januari 2022, terdapat kurang dari 200 laporan wabah LSD, dan pada periode ini, sebagian besar laporan berasal dari Rusia. Menariknya, tercatat bahwa pada 2015-2016, wabah di Rusia hanya dikaitkan dengan isolat lapangan LSDV, dan pada 2017, tidak hanya galur LSDV lapangan, tetapi juga galur LSDV mirip vaksin, menyebabkan beberapa wabah. Selanjutnya, epidemi 2018 terutama disebabkan oleh isolat seperti vaksin rekombinan [56,57]. Menurut temuan ini, disarankan bahwa penggunaan vaksin LSD hidup yang dilemahkan di Kazakhstan, negara tetangga Rusia, mungkin telah berkontribusi pada invasi dan penyebaran strain mirip vaksin LSDV ke Rusia [56,57].

Di Asia, Turki melaporkan banyak wabah LSD dari tahun 2013 hingga 2016 (Gambar4). Tren peningkatan LSD di Turki sejak 2013 telah dijelaskan sebelumnya. Di Turki, meskipun telah menggunakan vaksin, jumlah wabah meningkat, dan kemudian ditemukan bahwa strain Bakirkoy tidak efisien dalam mengendalikan LSD [13]. Kemudian, dianjurkan untuk menggunakan vaksin homolog [55,58]. Saat vaksin jenis ini digunakan, jumlah wabah mulai menurun, dan LSD akhirnya dieliminasi dari Turki. Diperkirakan bahwa penyakit ini menyebar dari Turki ke Irak dan Iran dengan melintasi perbatasan [19,59], mengakibatkan wabah tertinggi ditemukan di Irak pada tahun 2019 [59]. Pada pertengahan Juli 2019, wabah LSD terjadi di Bangladesh [60]. Segera setelah itu, Republik Rakyat Tiongkok melaporkan wabah pada minggu pertama Agustus 2019. Pada minggu kedua Agustus, wabah terjadi di India. Semua wabah ini sesuai dengan poin perubahan ketiga dan keempat, serta segmen keempat. Pada tahun 2020, negara-negara, termasuk Nepal, Sri Lanka, Bhutan, Vietnam, dan Myanmar, melaporkan wabah LSD ke WOAH [60]. Menyusul titik perubahan keempat, segmen kelima menunjukkan sedikit peningkatan laporan dari tahun 2020 hingga 2021. Temuan ini menunjukkan bahwa Thailand memiliki jumlah laporan wabah LSD tertinggi dibandingkan negara lain di Asia pada tahun 2021. Karena baru pertama kali Thailand menghadapi ancaman ini, wabah LSD ditemukan pada ternak sapi di seluruh negeri, menyebabkan kerugian ekonomi yang serius bagi industri ternak [25,61].

Dalam studi ini, kami menerapkan model ARIMA dan NNAR untuk meramalkan jumlah laporan wabah LSD. Secara keseluruhan, jumlah wabah di Afrika diperkirakan lebih tinggi dari yang dilaporkan pada 2020-2021, sedangkan jumlah wabah di Eropa diproyeksikan tetap konsisten. Prakiraan wabah LSD di Asia menunjukkan tren yang meningkat pada tahun 2023–2024 berdasarkan model NNAR, sedangkan ARIMA memprediksi jumlah wabah yang lebih besar daripada yang terjadi pada Januari 2022. Secara khusus, hasil menunjukkan bahwa kemampuan prediksi model ARIMA dan NNAR diuji dengan data Afrika tidak terlalu akurat, yang mungkin dipengaruhi oleh terbatasnya jumlah pengamatan yang digunakan untuk pelatihan model. Studi tindak lanjut dengan lebih banyak pengamatan akan memungkinkan pengembangan model model perkiraan yang lebih akurat. Lebih-lebih lagi, hasil kami mengungkapkan bahwa kemampuan prediksi ARIMA dan NNAR kira-kira sebanding. Hal ini mungkin disebabkan oleh fakta bahwa kumpulan data berisi pola linier dan non-linier, dan oleh karena itu, kekuatan satu model mungkin tidak memberikan keunggulan dibandingkan yang lain [37,45].

Prakiraan kami menawarkan informasi bermanfaat kepada pihak berwenang yang dapat dimasukkan ke dalam strategi untuk memantau dan mencegah wabah LSD di masa mendatang. Sebagai catatan, prakiraan dihasilkan dari pengamatan sebelumnya; dengan demikian, mereka tidak memperhitungkan situasi atau implementasi apa pun di masa depan. Jika intervensi seperti langkah-langkah pengendalian yang lebih efektif diadopsi, kemungkinan laporan KLB akan diterima lebih sedikit daripada yang diantisipasi. Dalam aspek ini, kami menyarankan untuk menggunakan

angka perkiraan sebagai informasi dasar atau tolok ukur, dengan tujuan menjaga jumlah wabah di bawah angka tersebut.

Studi saat ini memiliki beberapa keterbatasan. Kami tidak dapat menentukan karakteristik musiman dari jumlah laporan wabah LSD karena format dua tahunan dari data yang tersedia. Oleh karena itu, akan bermanfaat untuk penelitian selanjutnya jika data dari WOAH dipublikasikan dalam format bulanan. Selain itu, penting untuk dicatat bahwa hasil ramalan harus ditafsirkan dengan hati-hati. Karena prakiraan didasarkan pada pengamatan dan pola sebelumnya, beberapa intervensi dan perubahan pada penggerak penyakit di masa mendatang, yang dapat mengubah pola, akan berdampak pada kejadian penyakit yang sebenarnya, dan oleh karena itu, prakiraan kami mungkin terlalu tinggi atau terlalu rendah. Selain itu, mungkin ada pelaporan wabah LSD yang kurang di beberapa negara selama periode tertentu, sehingga laporan yang digunakan dalam penelitian ini mungkin tidak mewakili situasi yang sebenarnya. Lebih-lebih lagi, peramalan terbatas pada dua metode. Dengan demikian, studi tindak lanjut untuk menyelidiki metode lain untuk memperkirakan jumlah laporan wabah LSD diperlukan.

Perlu dicatat bahwa isolat LSDV dari wabah di beberapa negara terkait secara genetik [22,62, 63]; oleh karena itu, kerjasama internasional sangat penting untuk mengembangkan pengawasan regional untuk memantau, mengendalikan, dan mencegah serangan penyakit. Kolaborasi tersebut juga harus mencakup berbagi data terkait wabah LSD di setiap negara, seperti data epidemiologis dan informasi genetik LSDV.

5. Kesimpulan

Dalam karya ini, kami menggunakan pendekatan statistik untuk mengidentifikasi perubahan besar dalam data yang mendasari laporan wabah LSD. Selain itu, kami menggunakan model deret waktu untuk memperkirakan jumlah laporan wabah LSD di Afrika, Eropa, dan Asia selama 2022–2024. Meskipun laporan wabah LSD di Afrika tampak menurun sejak tahun 2020, diperkirakan jumlah laporan akan sedikit meningkat. Jumlah laporan wabah LSD di Eropa diproyeksikan melanjutkan tren stabil 5 tahun sebelumnya. Selain itu, perkiraan memprediksi peningkatan jumlah laporan wabah di Asia. Temuan ini menunjukkan bahwa LSD tetap menjadi ancaman besar bagi industri peternakan sapi di berbagai negara; dengan demikian, upaya harus dilakukan untuk memantau penyebarannya di dalam dan antar daerah. Selain itu, karena LSD dianggap sebagai penyakit lintas batas yang signifikan, pencegahan dan pengendalian penyakit yang ketat di setiap negara sangat penting. Selain itu, koordinasi antar negara untuk mengendalikan dan memberantas penyakit ini sangat penting.

Kontribusi Penulis: Konseptualisasi, VP, NP dan KN-L.; metodologi, VP, NP dan KN-L.; perangkat lunak, VP dan AA; validasi, VP, KN-L. dan NP; analisis formal, VP dan AA; sumber daya, VP dan NP; kurasi data, VP, AA dan KN-L.; menulis—persiapan draft asli, VP dan A A; menulis—review dan editing, VP, KN-L. dan NP; visualisasi, VP, AA, KN-L. dan NP; pengawasan, VP; administrasi proyek, VP; akuisisi pendanaan, VP Semua penulis telah membaca dan menyetujui versi naskah yang diterbitkan.

Pendanaan: Para penulis berterima kasih atas dana penelitian dari Center of Excellence in Veterinary Public Health dan Excellence Centre in Veterinary Bioscience, Universitas Chiang Mai, Chiang Mai 50200, Thailand.

Pernyataan Dewan Peninjau Kelembagaan: Tak dapat diterapkan.

Pernyataan Persetujuan yang Diinformasikan: Tak dapat diterapkan.

Pernyataan Ketersediaan Data: Data yang digunakan dalam penelitian ini dapat diakses oleh publik di website resmi WOAH (https://wahis.woah.org, diakses pada 14 Agustus 2022).

Konflik kepentingan: Para penulis menyatakan tidak ada konflik kepentingan. Selain itu, penyandang dana tidak memiliki peran dalam desain penelitian; dalam pengumpulan, analisis, atau interpretasi data; dalam penulisan naskah; atau dalam keputusan untuk mempublikasikan hasil.

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WILEY

TINJAUAN

Lumpy Skin Disease, penyakit virus lintas batas yang muncul: Tinjauan

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Abstrak

Lumpy Skin Disease adalah penyakit virus sapi yang muncul, yang endemik di sebagian besar negara Afrika dan beberapa negara di Timur Tengah, dan peningkatan risiko penyebaran penyakit ke seluruh Asia dan Eropa harus dipertimbangkan. Penyebaran penyakit yang cepat baru-baru ini di negara-negara yang saat ini bebas penyakit menunjukkan pentingnya memahami batasan dan rute distribusi. Agen penyebab, Capripoxvirus, juga dapat menyebabkan cacar domba dan cacar kambing. Signifikansi ekonomi dari penyakit ini sangat memprihatinkan, mengingat penyakit ini mengancam perdagangan internasional dan dapat digunakan sebagai agen bioterorisme ekonomi. Distribusi capripoxvirus tampaknya meluas karena terbatasnya akses ke vaksin yang efektif dan kemiskinan dalam komunitas petani. Hal ini sebagian besar disebabkan oleh dampak ekonomi dari pandemi Covid-19 dan pengenaan sanksi yang melumpuhkan di daerah endemik, serta peningkatan perdagangan legal dan ilegal hewan hidup dan produk hewan, serta perubahan iklim global. Tinjauan ini dirancang untuk memberikan informasi yang ada tentang berbagai aspek penyakit seperti klinikopatologi, penularan, epidemiologi, diagnosis, tindakan pencegahan dan pengendalian, dan potensi peran satwa liar dalam penyebaran penyakit lebih lanjut.

KATA KUNCI

capripox, epidemiologi, *Lumpy Skin Disease*, penyakit lintas batas

1 | PERKENALAN

Lumpy skin disease (LSD), ancaman utama bagi peternakan, dapat menyebabkan penyakit akut atau subakut pada sapi dan kerbau (Givens, 2018; Tuppurainen, Venter, et al., 2017). Semua umur dan ras sapi terpengaruh, tetapi terutama sapi muda dan sapi di puncak laktasi (Tuppurainen et al., 2011).

Alasan mengapa Organisasi Kesehatan Hewan Dunia (OIE) menempatkan penyakit lintas batas ini pada daftar penyakit yang harus dilaporkan adalah karena kerugian ekonomi yang signifikan dan potensi penyebaran yang cepat (Tuppurainen & Oura, 2012). Penyebaran penyakit baru-baru ini di negara-negara bebas penyakit menunjukkan pentingnya penularannya, serta pengendalian dan pemberantasannya (Sprygin et al., 2019). Lumpy skin disease virus (LSDV) adalah DNA beruntai ganda yang mengandung sekitar 150 kilobase pair (kbp) dengan ukuran relatif besar (230–260 nm), terbungkus dalam selubung lipid dan termasuk dalam genus Capripoxvirus, yang secara genetik berkerabat dengan domba. cacar (SPPV) dan virus cacar kambing (GTPV) (Bhanuprakash et al., 2006; Buller et al., 2005; Givens, 2018). Virus ini adalah yang paling signifikan secara ekonomi dalam keluarga Poxviridae yang mempengaruhi ruminansia domestik. Kapsid atau nukleokapsid virus berbentuk bata atau oval yang mengandung genom dan badan lateral. Hibridisasi silang DNA yang ekstensif antar spesies menyebabkan reaksi silang serologis

dan perlindungan silang antar anggota. Meskipun Capripoxvirus umumnya dianggap spesifik inang, strain SPPV dan GTPV dapat secara alami atau eksperimental menginfeksi silang dan menyebabkan penyakit pada kedua spesies inang. Sebaliknya, LSDV secara eksperimental dapat menginfeksi domba dan kambing, tetapi tidak ada infeksi alami pada domba dan kambing yang dilaporkan dengan LSDV.

2 | KOPATOLOGI CL INI

Gambaran klinis dari penyakit ini meliputi demam, kurang nafsu makan, keluarnya cairan dari hidung, air liur dan lakrimasi, pembesaran kelenjar getah bening, penurunan produksi susu yang cukup besar, penurunan berat badan dan terkadang kematian (Abutarbush et al., 2013; Annandale et al., 2014 ; Babiuk et al., 2008; Tasioudi et al., 2016). Selain itu, penyakit ini ditandai dengan nodul kulit yang tegas, sedikit menonjol, berbatas tegas (Gambar 1) dengan diameter 2–7 cm dan biasanya muncul di leher, kaki, ekor, dan punggung, segera setelah awal demam (Beard, 2016 ; Sevik & Dogan, 2017). Nodul nekrotik dan ulseratif meningkatkan risiko myiasis (Beard, 2016). Edema kaki dan ketimpangan diamati dalam beberapa kasus (Tuppurainen & Oura, 2012). LSDV dapat menyebabkan aborsi (Radostitis et al., 2006), mastitis dan orkitis (Awadin et al., 2011). Namun, nodul tidak diamati pada janin yang diaborsi (Sevik & Dogan, 2017). Dengan nekropsi, edema paru dan kongesti, nodul di seluruh paru-paru dan saluran pencernaan sering diamati (Zeynalova et al., 2016). Jaringan seperti moncong, rongga hidung, laring, trakea, bagian dalam bibir, bantalan gigi, gingiva, abomasum, ambing, puting susu, rahim, vagina dan testis mungkin akan terpengaruh. Komplikasi penyakit parah dilaporkan sebagai keratitis, disentri, ketimpangan, pneumonia, mastitis dan myiasis (Al-Salihi & Hassan, 2015; Tuppurainen et al., 2017). bantalan gigi, gingiva, abomasum, ambing, puting susu, rahim, vagina dan testis mungkin terpengaruh. Komplikasi penyakit parah dilaporkan sebagai keratitis, disentri, ketimpangan, pneumonia, mastitis dan myiasis (Al-Salihi & Hassan, 2015; Tuppurainen et al., 2017). bantalan gigi, gingiva, abomasum, ambing, puting susu, rahim, vagina dan testis mungkin terpengaruh. Komplikasi penyakit parah dilaporkan sebagai keratitis, disentri, ketimpangan, pneumonia, mastitis dan myiasis (Al-Salihi & Hassan, 2015; Tuppurainen et al., 2017).

Pemeriksaan histopatologis nodul kulit dapat mengungkapkan badan inklusi intrasitoplasma eosinofilik eosinofilik yang patognomonik dalam keratinosit, makrofag, sel endotel dan pericytes dan berhubungan dengan degenerasi balon sel spinosum.

GAMBAR 1 Penyakit kulit berlendir. Dibesarkan, nodular berbatas tegas luka

Infiltrasi jaringan kulit superfisial pada area yang terkena oleh sel inflamasi seperti makrofag, limfosit, dan eosinofil terlihat. Selain itu, vaskulitis luas dan nekrosis koagulatif parah pada otot subkutan dapat diamati pada beberapa kasus (Constable et al., 2017; Sevik et al., 2016). Penyakit kulit semu, urtikaria, streptotrikosis (Dermatophilus congolensisinfeksi), kurap,Hipoderma bovisinfeksi, fotosensitisasi, bovine papular stomatitis, penyakit kaki dan mulut, diare virus bovine, dan demam catarrhal maligna semuanya dipertimbangkan dalam diagnosis banding LSD (Abutarbush, 2017).

3 | PATOGEN ADALAH

Setelah infeksi LSDV, replikasi virus, viremia, demam, lokalisasi virus di kulit dan perkembangan nodul terjadi (Constable et al., 2017). Secara eksperimental, setelah inokulasi virus intradermal, kejadian berikut dilaporkan:

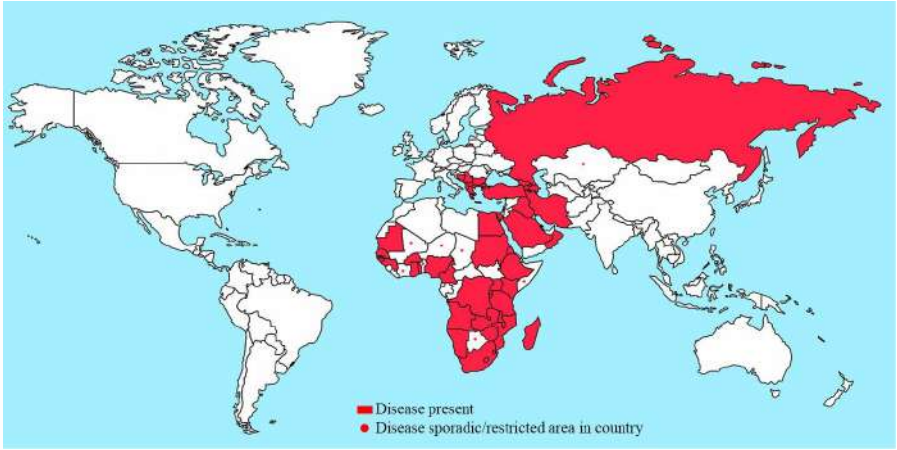
- 4 sampai 7 hari pasca infeksi (DPI): pembengkakan lokal sebagai nodul berukuran 1–3 cm atau plak di tempat inokulasi
- 6 hingga 18 DPI: viremia dan pelepasan virus melalui sekret mulut dan hidung
- 7 sampai 19 DPI: limfadenopati regional dan perkembangan nodul kulit umum
- 42 hari setelah demam: adanya virus dalam air mani (Coetzer, 2004).

Replikasi virus intraseluler dalam fibroblas, makrofag, perisit, dan sel endotel menyebabkan vaskulitis dan limfangitis pada jaringan yang terkena (Coetzer, 2004).

Tampaknya pedet muda, sapi laktasi dan hewan kurus lebih rentan terhadap infeksi alami, mungkin karena penurunan imunitas humoral (Babiuk, Bowden, Boyle, et al., 2008). Hewan yang telah pulih dari infeksi alami oleh virus telah menunjukkan kekebalan seumur hidup. Pedet dari induknya yang terinfeksi resisten terhadap penyakit klinis selama kurang lebih 6 bulan karena antibodi maternal yang didapat (Tuppurainen et al., 2005). Hewan yang terkena menghilangkan infeksi dan belum ada negara pembawa LSDV yang diketahui (Tuppurainen, Alexandrov, et al., 2017).

4 | PENULARAN

Penyakit kulit yang menggumpal dapat menyerang sapi, kerbau, dan ruminansia liar. Tampaknya domba dan kambing tidak terinfeksi oleh virus tersebut (El-Nahas et al., 2011; Lamien, Le Goff, et al., 2011). LSDV dapat tetap hidup untuk waktu yang lama di lingkungan pada suhu sekitar, terutama pada keropeng kering. Dilaporkan bahwa virus bertahan di nodul kulit nekrotik hingga 33 hari atau lebih, di kerak kering hingga 35 hari dan setidaknya 18 hari di kulit yang dikeringkan dengan udara. Virus dapat diinaktivasi pada suhu 55°C selama 2 jam dan 65°C selama 30 menit (Mulatu & Feyisa, 2018). Sumber utama infeksi dianggap lesi kulit karena virus bertahan di lesi atau keropeng untuk waktu yang lama.



GAMBAR 2 Situasi global penyakit kulit menggumpal (FAO, 2016)

Virus ini juga diekskresikan melalui darah, sekresi hidung dan air mata, air liur, air mani dan susu (dapat menular ke anak sapi yang menyusu).

LSDV ditularkan melalui arthropoda, terutama serangga penghisap darah (Chihota, Rennie, Kitching, & Mellor, 2001, 2003; MacLachlan & Dubovi, 2011), pakan dan air yang terkontaminasi dan transmisi langsung pada tahap akhir penyakit melalui air liur, sekresi hidung dan air mani (Annandale et al., 2014; Chihota et al., 2001; Irons et al., 2005; Tuppurainen, Venter, et al., 2017). Beberapa penelitian menunjukkan tidak ada korelasi positif antara kepadatan ternak dan tingkat infeksi, menunjukkan rendahnya pentingnya penularan virus langsung, setidaknya pada tahap awal penyakit, dibandingkan dengan penularan tidak langsung yang signifikansinya lebih tinggi (Carn & Kitching, 1995; Magori-Cohen et al., 2012).

Karena sebagian besar wabah LSD terjadi pada musim panas ketika arthropoda paling aktif, ini mungkin mengindikasikan keterlibatan berbagai spesies vektor, terutama serangga pemakan darah, dalam penyebaran virus (Kahana-Sutin et al., 2017; Sprygin et al., 2018).

Beberapa penelitian telah menyarankan kemungkinan peran kutu keras dalam penularan virus (Lubinga et al., 2015; Tuppurainen et al., 2011, 2013). Virus *Lumpy Skin Disease* dan antigen virus ditemukan dalam air liur dan berbagai organ kutu, termasuk hemosit, kelenjar ludah dan usus tengah dalam air liur dan berbagai organ kutu seperti hemosit, kelenjar ludah dan usus tengah (Lubinga et al., 2013, 2014). Selanjutnya, penularan virus secara transstadial dan mekanis oleh kutu dibuktikan berdasarkan bukti molekuler (Tuppurainen & Oura, 2012). Namun, keterikatan mereka yang berkepanjangan dengan inang tidak menjelaskan terjadinya epidemi yang luas dengan cepat. Oleh karena itu, tampaknya kutu dapat berperan sebagai reservoir virus (Kahana-Sutin et al., 2017).

Aedes aegyptiadalah satu-satunya dipteran yang mampu menularkan virus sepenuhnya ke ternak yang rentan (Chihota et al., 2001). Nyamuk seperti Culicoides nubeculosus,Culex quinquefasciatusKatakan danAnopheles stephensiListon tidak dapat menularkan virus (Chihota et al., 2003).

MeskipunKalsitrans stomoxystelah terlihat pada wabah LSD dan telah menularkan virus capripox ke domba dan kambing (Baldacchino et al.,
2013; Yeruham et al., 1995), penularan LSDV ke hewan yang rentan telah gagal (Chihota et al., 2003). Sejak LSDV telah terdeteksi diCulicoides punctatus, itu mungkin berperan dalam penularan virus (Sevik & Dogan, 2017). Dinyatakan pula bahwa rasio dari gigitan serangga ke populasi inang berkorelasi positif dengan kemungkinan penularan (Gubbins et al., 2008).

Dalam studi eksperimental, persistensi virus *Lumpy Skin Disease* diindikasikan dalam semen sapi oleh PCR dan isolasi virus (Annandale et al., 2010; Givens, 2018; Irons et al., 2005). Juga, air mani menyebabkan penularan virus ke sapi dara yang diinseminasi (Annandale et al., 2014).

5| EPIDEMIOLOGI

5.1| Distribusi geografis

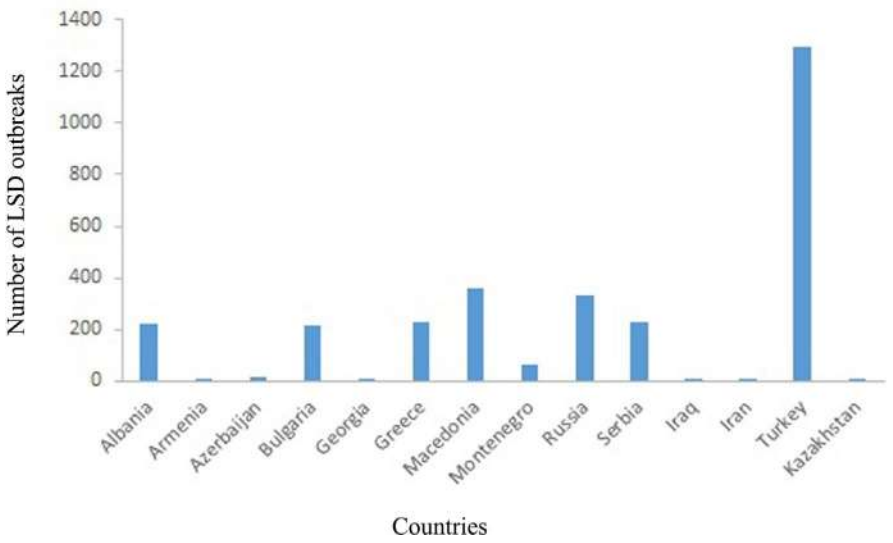
LSDV didiagnosis pertama kali di Zambia pada tahun 1929 dan kemudian dilaporkan di beberapa wilayah negara Afrika (Wainwright et al., 2013). Penyakit ini telah diidentifikasi di Arab Saudi, Lebanon, Yordania, Irak, Israel, Turki dan Iran (Abutarbush et al., 2013; Al-Salihi & Hassan, 2015; Ben-Gera et al., 2015; Ince et al., 2016; Sameea Yousefi et al., 2017). Sejak 2015, telah menyebar ke Rusia, Azerbaijan, Armenia, Yunani dan Bulgaria, Albania, Kosovo, Serbia, dan Montenegro (Beard, 2016; EFSA, 2017; OIE, 2015; Ripani & Pacholek, 2015; Tasioudi et al., 2016; Wainwright et al., 2013; Zeynalova et al., 2016). Oleh karena itu, peningkatan risiko penyebaran penyakit ke seluruh Eropa dan Asia harus dipertimbangkan (Gambar 2).

Jumlah wabah penyakit kulit menggumpal di berbagai negara dilaporkan pada tahun 2014–2016 oleh OIE (Gambar 3). Misalnya, jumlah wabah LSD di beberapa negara Timur Tengah dengan batas yang luas masing-masing adalah 6, 8, 1.294, 1, 16, 1, dan 330 di Iran, Irak, Turki, Kazakstan, Azerbaijan, Armenia, dan Rusia (OIE WAHID, 2018).

5.2| Morbiditas dan mortalitas

Belum ada laporan mengenai masa inkubasi infeksi LSDV pada kondisi lapangan (OIE, 2018). Meskipun tingkat morbiditas

GAMBAR 3 Jumlah wabah LSD di berbagai negara selama 2014–2016 (OIE, 2018)



bervariasi antara 5% dan 45% (kadang sampai 100%), angka kematian biasanya di bawah 10% (kadang sampai 40%) (Coetzer, 2004). Misalnya, tingkat morbiditas dan mortalitas wabah dilaporkan masing-masing 8,7% dan 0,4%, di Yunani (Tasioudi et al., 2016) dan 12,3% dan 6,4%, di Turki (Sevik & Dogan, 2017). Tingkat keparahan penyakit klinis sering dipengaruhi oleh umur hewan, ras, status kekebalan dan periode produksi (Tuppurainen, Venter, et al., 2017).

5.3 | Faktor risiko

Faktor risiko yang terkait dengan penyebaran LSD termasuk iklim yang hangat dan lembab, kondisi yang mendukung kelimpahan populasi vektor, seperti yang terlihat setelah hujan musiman, dan masuknya hewan baru ke kawanan.

Ukuran kawanan, populasi vektor, jarak ke danau, migrasi kawanan, pengangkutan hewan yang terinfeksi ke daerah bebas penyakit, padang rumput umum dan sumber air semuanya telah dianggap sebagai faktor risiko lain, yang dapat meningkatkan prevalensi penyakit (Gari et al. ., 2010; Ince et al., 2016; Sevik & Dogan, 2017). Selain itu, arah dan kekuatan angin kemungkinan berkontribusi terhadap penyebaran virus (Chihota et al., 2003; Rouby & Aboulsoud, 2016).

Semua umur dan ras ternak, serta kedua jenis kelamin, rentan terhadap penyakit ini (Tuppurainen et al., 2011). Selain itu, faktor risiko yang terkait dengan seropositif LSDV meliputi usia, jenis kelamin, jenis pengelolaan, curah hujan tahunan rata-rata, dan sumber air umum (Ochwo et al., 2019).

5.4 | Peran satwa liar dalam penyebaran penyakit

Seropositif dapat menunjukkan kemungkinan peran hewan dalam epidemiologi penyakit (Barnard, 1997). Sepertinya ringan kasus klinis pada satwa liar mudah terlewatkan karena sulit atau tidak mungkin untuk memantau lesi kulit (Barnard, 1997).

Kerentanan springbok, impala dan jerapah terhadap virus telah dibuktikan (Lamien, Le Goff, et al., 2011; Le Goff et al., 2009; Young et al., 1970). Spesies lain yang seropositif untuk virus ini termasuk kerbau Afrika, rusa kutub biru, eland, jerapah, impala dan kudu besar (Barnard, 1997; Davies, 1982; Fagbo et al., 2014). Penyakit ini dilaporkan pada kijang Arab oleh Greth et al., (1992). Namun, peran satwa liar dalam epidemiologi LSD belum dipahami dengan baik (Tuppurainen, Venter, et al., 2017).

6 | DAMPAK EKONOMI C

Lumpy Skin Disease telah menyebabkan kerugian ekonomi yang serius di negara-negara yang terkena dampak. Penyakit ini menyebabkan penurunan produksi susu yang cukup besar (dari 10% menjadi 85%) karena demam tinggi dan mastitis sekunder. Konsekuensi lain dari penyakit ini termasuk kerusakan kulit, penurunan tingkat pertumbuhan sapi potong, kemandulan sementara atau permanen, aborsi, biaya perawatan dan vaksinasi dan kematian hewan yang terinfeksi (Alemayehu et al., 2013; Babiuk, Bowden, Boyle, et al. ., 2008; Sajid et al., 2012; Sevik & Dogan, 2017). Total biaya wabah LSD pada 393 ternak yang disurvei adalah 822.940,7 GBP di Turki (Sevik & Dogan, 2017). Di Ethiopia, perkiraan kerugian finansial masing-masing adalah 6,43 USD dan 58 USD per ekor untuk zebu lokal dan Holstein Friesian (Gari et al., 2010). Total kerugian produksi akibat penyakit ini diperkirakan mencapai 45%–65% dalam industri peternakan sapi (Tuppurainen & Oura, 2012). Agen penyebab, capripoxvirus, juga dapat menyebabkan cacar domba dan cacar kambing, dan penyakit ini memiliki signifikansi ekonomi, mengingat bahwa penyakit ini merupakan hambatan utama bagi perdagangan internasional dan dapat disalahgunakan sebagai agen bioterorisme ekonomi.

TABEL 1 Teknik berbeda untuk diagnosis LSD

Teknik	Tujuan		Kontribusi di kebijakan pemberantasan	Konfirmasi dari kasus klinis	Prevalensi surveilans infeksi	Status kekebalan pasca vaksinasi
	Hewan bebas dari infeksi	Hewan bebas dari infeksi sebelum dipindahkan				
Identifikasi agen						
Isolasi virus	+	+ +	+	+ + +	+	-
PCR	+ +	+ + +	+ +	+ + +	+	-
Mikroskop elektron	-	-	-	+	-	-
Deteksi respons imun						
Netralisasi virus	+ +	+ +	+ +	+ +	+ +	+ +
Mikroskop elektron	+	+	+	+	+	+

Catatan: -:tidak sesuai dengan tujuannya; +: dapat digunakan dalam beberapa situasi, tetapi penerapannya dibatasi oleh beberapa faktor seperti keandalan, biaya, dll.; ++: metode yang sesuai; +++: metode yang disarankan.
IFAT menunjukkan Tes Antibodi Pendar Tidak Langsung; dan PCR, reaksi berantai polimerase.

Meskipun diagnosis klinis utama LSD, diagnosis dikonfirmasi dengan menggunakan PCR konvensional (Orlova et al., 2006; Tuppurainen et al., 2005; Zheng et al., 2007) atau teknik PCR real-time (Balinsky et al., 2008; Bowden et al., 2008). Teknik PCR real-time juga telah ditetapkan, membedakan antara LSDV, virus cacar domba dan kambing (Lamien, Lelenta, et al., 2011). Untuk membedakan LSDV virulen dari galur vaksin, Restriction Fragment Length Polymorphism (RFLP) juga telah digunakan (Menasherow et al., 2014). Selanjutnya, mikroskop elektron, isolasi virus, netralisasi virus, dan teknik serologi telah digunakan untuk deteksi LSDV seperti yang ditunjukkan pada Tabel 1 (OIE, 2018). Disebutkan bahwa metode molekuler lebih tepat, handal dan cepat dibandingkan dengan metode lainnya (Stubbs et al., 2012). Di antara teknik serologis, tes netralisasi virus, yang lambat dan mahal dengan spesifisitas tinggi dan sensitivitas rendah, adalah satu-satunya tes yang saat ini divalidasi/valid (Beard, 2016). Babiuk, Bowden, Parkyn, dkk. (2008) mendirikan deteksi imunohistokimia antigen LSDV dalam studi eksperimental.

Terlepas dari spesifisitas dan sensitivitas tes western blot, itu mahal dan sulit dilakukan (OIE, 2018).

8 | PENCEGAHAN DAN PENGENDALIAN

Penyebaran capripoxvirus tampaknya meluas karena terbatasnya akses ke vaksin yang efektif dan kemiskinan masyarakat petani di daerah endemik, serta meningkatnya perdagangan hewan hidup secara legal dan ilegal, selain perubahan iklim global. Vaksinasi adalah satu-satunya metode yang efektif untuk mengendalikan penyakit di daerah endemik bersamaan dengan pembatasan pergerakan dan pemindahan hewan yang terkena (Sevik & Dogan, 2017). Pengobatan LSD hanya simtomatik dan ditargetkan untuk mencegah komplikasi bakteri sekunder menggunakan kombinasi antimikroba, antiinflamasi, terapi suportif dan larutan antiseptik (Salib & Osman, 2011). Pemusnahan hewan yang terkena dampak, pembatasan pergerakan dan vaksinasi wajib dan konsisten telah direkomendasikan sebagai strategi pengendalian (Beard, 2016; OIE WAHIS, 2016; Tuppurainen, Venter, et al., 2017). Namun, terkait peran vektor arthropoda, pemberantasan penyakit ini kemungkinan akan sulit dan penundaan pemusnahan hewan yang terinfeksi meningkatkan risiko penularan LSD (Tuppurainen, Venter, et al., 2017). Selain itu, faktor risiko harus dipertimbangkan dalam aktivitas pengendalian (Sevik & Dogan, 2017). Mendidik dokter hewan dan pekerja ternak akan memungkinkan mereka untuk melakukan diagnosis kasus klinis secara tepat waktu, membantu memperlambat penyebaran penyakit (Beard, 2016).

Anggota capripoxvirus diketahui memberikan perlindungan silang. Oleh karena itu, vaksin hidup yang dilemahkan homolog (Neethling LSDV) dan heterolog (virus cacar domba atau kambing) semuanya dapat digunakan untuk melindungi sapi terhadap infeksi LSD (OIE, 2013). Di negara-negara bebas LSD yang menggunakan vaksin cacar domba untuk melindungi domba dari cacar domba, dianjurkan untuk menggunakan vaksin yang sama selama wabah LSD karena potensi masalah keamanan terkait dengan

penggunaan vaksin LSDV hidup yang dilemahkan (Tuppurainen & Oura, 2012). Selain itu, konfirmasi diagnosis klinis yang cepat sangat penting sehingga langkah-langkah pemberantasan, seperti karantina, penyembelihan hewan yang terkena dan kontak, pembuangan bangkai yang tepat, pembersihan dan disinfeksi tempat, dan pengendalian serangga dapat diterapkan sebagaimana mestinya. sesegera mungkin selama letusan (Constable et al., 2017; Tuppurainen et al., 2005). Selain itu, pembatasan impor yang ketat terhadap ternak, bangkai, kulit, dan semen dari daerah endemik harus diberlakukan di daerah bebas penyakit (Sevik & Dogan, 2017).

Diketahui bahwa kekebalan lengkap terhadap LSD tidak diberikan oleh vaksin cacar domba bekas (Brenner et al., 2009). Namun demikian, mereka digunakan di beberapa negara seperti Irak, Iran, Turki dan negara-negara Afrika dengan tumpang tindih antara LSD, SPP dan GTP (Sameea Yousefi et al., 2017).

Vaksin LSD yang tersedia secara komersial adalah vaksin hidup yang dilemahkan. Meskipun lesi kulit telah berkembang pada beberapa hewan yang divaksinasi setelah terpapar virus, ada lebih banyak kasus klinis pada kawanan yang tidak divaksinasi dibandingkan dengan kawanan yang divaksinasi (Brenner et al., 2009; Stram et al., 2008). Vaksin murah ini dapat memberikan perlindungan yang memadai melalui program vaksinasi tahunan (Tuppurainen, Venter, et al., 2017). Saat ini, keamanan dan kemanjuran vaksin inaktif yang baru dikembangkan telah dikonfirmasi dalam studi lapangan oleh Hamdi et al. (2020).

Vaksin hidup menghasilkan respon imun yang kuat dan tahan lama, serta efisien dalam pengendalian penyebaran penyakit (Tuppurainen et al., 2020). Namun, vaksin hidup dapat menyebabkan peradangan lokal dan penyakit ringan dengan lesi kulit (Bedekovic et al., 2017). Meskipun vaksin yang tidak aktif mahal dan memerlukan beberapa pemberian, vaksin tersebut aman dan memungkinkan untuk menggabungkannya dengan antigen lain untuk membuat vaksin polivalen yang dapat digunakan di negara bebas penyakit. Selain itu, vaksin inaktif dapat diterapkan pada tahap akhir pemberantasan penyakit sebagai bagian dari strategi yang menggunakan vaksin hidup terlebih dahulu (Hamdi et al., 2020).

Karena ada kemungkinan rekombinasi antara strain liar dan vaksin hidup, risiko koinfeksi harus dipertimbangkan dengan penggunaan vaksin hidup (Sprygin et al., 2018). Infeksi alami mungkin diperparah dengan vaksinasi hewan yang terinfeksi (Sprygin et al., 2019). Juga, vaksin ini tidak direkomendasikan di negara bebas penyakit. Pembedaan yang terinfeksi dari hewan yang divaksinasi (DIVA) harus dikembangkan untuk negara non-endemik, ini juga akan menjadi alat yang efektif untuk negara endemik (Tuppurainen, Venter, et al., 2017).

9 | KESIMPULAN

Penyebaran penyakit baru-baru ini ke daerah bebas penyakit menunjukkan signifikansi epidemiologis dan ekonominya. Mempertimbangkan luasnya perbatasan negara-negara Timur Tengah, pergerakan hewan di antara negara-negara ini harus dikontrol dengan hati-hati oleh otoritas veteriner. Selain itu, memperhatikan dengan seksama berbagai aspek penyakit, seperti penularan dan epidemiologi, dan penerapan langkah-langkah pencegahan yang efektif seperti vaksinasi, dapat menghasilkan pengendalian penyakit yang lebih baik. Oleh karena itu, diagnosis yang akurat dan tepat waktu di daerah endemik, vaksinasi dengan strain homolog LSDV, pengendalian vektor, pembatasan pergerakan hewan, dan pengujian LSDV pada pejantan yang digunakan untuk pembibitan sangat direkomendasikan sebagai alat untuk mengendalikan penyebaran lebih lanjut.

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Para penulis menghargai dukungan dari Universitas Shiraz.

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Para penulis menyatakan bahwa tidak ada konflik kepentingan.

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Mirror of Research in Veterinary Sciences and Animals (MRVSA)

Mengulas artikel

Lumpy Skin Disease: Tinjauan literatur

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Abstrak

Lumpy Skin Disease (LSD) menyebabkan kerugian ekonomi yang sangat besar pada industri peternakan. Penyakit ini disebabkan oleh virus penyakit kulit Lumpy (LSDV), yang termasuk dalam famili Poxviridae, dengan strain Neethling sebagai prototipe. LSDV milik genus Capripoxvirus yang mencakup virus cacar domba dan virus cacar kambing. LSD adalah penyakit menular enzootik, meletus dan jarang fatal pada ternak yang ditandai dengan nodul pada kulit. Sapi dan kerbau adalah satu-satunya spesies hewan yang terkena, dengan tingkat morbiditas yang tinggi, tetapi kematian yang rendah, namun tingkat kematian lebih tinggi di antara anak sapi. LSD menyebabkan hilangnya produksi susu dan daging sapi, aborsi pada wanita dan kemandulan pada pria. Fokus asli LSD berasal dari Zambia pada tahun 1929. LSD dianggap sebagai penyakit endemik di benua Afrika. Namun, penyakit ini telah berpindah ke luar Afrika pada tahun 1984. Dilaporkan di Madagaskar dan beberapa negara di Semenanjung Teluk Arab dan Timur Tengah. Baru-baru ini, penyakit tersebut dilaporkan di negara-negara bebas LSD (Yordania, Suriah, Lebanon, Turki, Iran dan Irak) dengan potensi kerugian ekonomi bagi industri peternakan. Artikel ulasan ini bermaksud untuk membahas LSD mengingat situasi terkini menimbulkan kekhawatiran penyebaran penyakit di negara-negara bebas LSD.

Kata kunci: *Lumpy Skin Disease*, sapi, knopvelsiekte, Timur Tengah.

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Perkenalan

Lumpy Skin Disease (LSD, Pseudo-urticaria, Neethling virus disease, exanthema nodularis bovis, dan knopvelsiekte) merupakan penyakit menular. Penyakit ini disebabkan oleh virus (LSDV) dalam keluarga Poxviridae, genus Capripoxvirus. Ini terkait erat secara antigenik dengan virus cacar domba dan kambing. Namun, virus ini tidak dapat dibedakan dengan menggunakan uji serologi rutin (Alexanderet al1957). LSD adalah penyakit sapi dan kerbau. Ini adalah penyakit yang ditularkan melalui vektor yang ditularkan oleh arthropoda penggigit dan penggigit darah yang berbeda. LSD Menyebabkan kerugian ekonomi yang cukup besar akibat kekurusan, kerusakan kulit, kemandulan, mastitis, hilangnya produksi susu, dan kematian hingga 20%. Tingkat keparahan tanda-tanda klinis LSD tergantung pada strain capripoxvirus dan breed sapi inang (Anonim 1988). Hingga tahun 1989, penyakit kulit lumpy terbatas pada

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Benua Afrika. Namun, penyakit tersebut berpindah ke luar Afrika ke Madagaskar dan Timur Tengah dan menyebabkan kerugian ekonomi yang serius bagi industri peternakan. Masa inkubasi di lapangan diyakini dua sampai lima minggu, dan lesi pertama kali muncul di tempat inokulasi dalam 4 sampai 20 hari. Demam adalah tanda awal yang diikuti dalam dua hari dengan perkembangan nodul pada kulit dan selaput lendir (Tuppurainen dan Oura 2012; Brenneret al2006). Diagnosis LSD dibuat berdasarkan pola klinis yang khas (morbiditas dan mortalitas). Diagnosis yang dikonfirmasi didasarkan pada mikroskop elektron transmisi (TEM), pewarnaan imunoperoksidase (IMP), uji imunosorben terkait enzim penangkap antigen (ELISA) dan uji reaksi berantai polimerase (PCR). Tidak ada pengobatan khusus untuk LSD. Namun, pengobatan suportif harus diberikan kepada hewan yang terinfeksi untuk menghilangkan tanda-tanda klinis dan untuk mengendalikan semua komplikasi sekunder. Imunisasi hewan yang rentan adalah metode yang efektif untuk mengendalikan penyakit di Afrika Selatan, dan vaksin yang efektif dihasilkan dari virus strain Neethling (Ayeletet al2014).

Organisme Penyebab

Genus Capripoxvirus dari famili Poxviridae adalah agen penyebab penyakit kulit Lumpy. Lumpy skin disease virus (LSDV) terkait erat secara antigenik dengan virus cacar domba dan kambing (Woods 1988). Walaupun ketiga virus ini berbeda, namun tidak dapat dibedakan dengan uji serologis rutin (Gambar 1). LSDV rentan terhadap 55°C/2 jam dan 65°C/30 menit. Itu dapat dipulihkan dari nodul kulit dan disimpan pada -80 ° C selama 10 tahun. Cairan kultur jaringan yang terinfeksi dapat disimpan pada suhu 4°C selama 6 bulan. Virus ini rentan terhadap pH yang sangat basa atau asam. Namun, tidak ada penurunan titer yang signifikan ketika ditahan pada pH 6,6-8,6 selama 5 hari pada suhu 37°C. LSDV rentan terhadap eter (20%), kloroform, formalin (1%), dan beberapa deterjen, misalnya natrium dodesil sulfat. Selain itu, juga rentan terhadap fenol (2%/15 menit), natrium hipoklorit (2–3%), senyawa yodium (pengenceran 1:33), Virkon® (2%) dan senyawa amonium kuarterner (0,5%). LSDV sangat stabil, bertahan dalam waktu lama pada suhu sekitar, terutama pada keropeng kering. LSDV sangat tahan terhadap inaktivasi. Itu bertahan dalam nodul kulit nekrotik hingga 33 hari atau lebih, kerak kering hingga 35 hari dan setidaknya 18 hari dalam kulit yang dikeringkan dengan udara. Itu dapat tetap bertahan untuk waktu yang lama di lingkungan. Sementara itu, virus rentan terhadap sinar matahari dan deterjen yang mengandung pelarut lipid, sedangkan pada kondisi lingkungan yang gelap, seperti kandang hewan yang terkontaminasi, dapat bertahan selama berbulan-bulan. Urutan genom LSDV diidentifikasi (Tulman bertahan dalam waktu lama pada suhu sekitar, terutama pada keropeng kering. LSDV sangat tahan terhadap inaktivasi. Itu bertahan dalam nodul kulit nekrotik hingga 33 hari atau lebih, kerak kering hingga 35 hari dan setidaknya 18 hari dalam kulit yang dikeringkan dengan udara. Itu dapat tetap bertahan untuk waktu yang lama di lingkungan. Sementara itu, virus rentan terhadap sinar matahari dan deterjen yang mengandung pelarut lipid, sedangkan pada kondisi lingkungan yang gelap, seperti kandang hewan yang terkontaminasi, dapat bertahan selama berbulan-bulan. Urutan genom LSDV diidentifikasi (Tulman bertahan dalam waktu lama pada suhu sekitar, terutama pada keropeng kering. LSDV sangat tahan terhadap inaktivasi. Itu bertahan dalam nodul kulit nekrotik hingga 33 hari atau lebih, kerak kering hingga 35 hari dan setidaknya 18 hari dalam kulit yang dikeringkan dengan udara. Itu dapat tetap bertahan untuk waktu yang lama di lingkungan. Sementara itu, virus rentan terhadap sinar matahari dan deterjen yang mengandung pelarut lipid, sedangkan pada kondisi lingkungan yang gelap, seperti kandang hewan yang terkontaminasi, dapat bertahan selama berbulan-bulan. Urutan genom LSDV diidentifikasi (Tulman Itu dapat tetap bertahan untuk waktu yang lama di lingkungan. Sementara itu, virus rentan terhadap sinar matahari dan deterjen yang mengandung pelarut lipid, sedangkan pada kondisi lingkungan yang gelap, seperti kandang hewan yang terkontaminasi, dapat bertahan selama berbulan-bulan. Urutan genom LSDV diidentifikasi (Tulman Itu dapat tetap bertahan untuk waktu yang lama di lingkungan. Sementara itu, virus rentan terhadap sinar matahari dan deterjen yang mengandung pelarut lipid, sedangkan pada kondisi lingkungan yang gelap, seperti kandang hewan yang terkontaminasi, dapat bertahan selama berbulan-bulan. Urutan genom LSDV diidentifikasi (Tulmanet al2001). Genom LSDV (151-kbp) terdiri dari daerah pengkodean pusat yang dibatasi

oleh pengulangan terminal terbalik 2,4 kbp yang identik dan berisi 156 gen diduga. Namun, chordopoxvirus dari genera lain mengungkapkan 146 gen yang dilestarikan, yang menyandikan protein yang terlibat dalam transkripsi dan biogenesis mRNA, metabolisme nukleotida, replikasi DNA, pemrosesan protein, struktur dan perakitan virion, serta virulensi virus dan kisaran inang. Gen LSDV berbagi kolinearitas tingkat tinggi dan identitas asam amino (rata-rata 65%) dari wilayah genomnya dengan gen poxvirus mamalia lain yang diketahui, terutama suipoxvirus, yatapoxvirus, dan leporipoxvirus. Kolinearitas terganggu dan homolog poxvirus tidak ada atau memiliki persentase identitas asam amino yang lebih rendah (rata-rata 43%) di daerah terminal.

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protein yang ditemukan dalam genera poxvirus lainnya. LSDV terkait erat dengan anggota lain dari Chordopoxvirinae, mengandung komplemen unik dari gen yang bertanggung jawab untuk kisaran inang dan virulensi virus. Urutan genom lengkap dari beberapa virus capripox, termasuk LSDV (Tulmanet al2001), virus poxvirus domba dan poxvirus kambing (Tulmanet al2002), telah diterbitkan.

Riwayat penyakit kulit yang menggumpal

Deskripsi pertama dari tanda-tanda klinis LSD adalah pada tahun 1929 di Zambia (sebelumnya Rhodesia Utara) (Morris 1931). Pada awalnya, tanda-tanda LSD dianggap sebagai akibat dari keracunan atau hipersensitivitas terhadap gigitan serangga. Tanda-tanda klinis yang sama juga terjadi di Botswana, Zimbabwe dan Republik Afrika Selatan antara tahun 1943 dan 1945, di mana sifat infeksi penyakit ini diakui dalam wabah tersebut.

Di Afrika Selatan, LSD terjadi sebagai panzootik, yang menyerang delapan juta sapi. Penyakit ini berlanjut sampai tahun 1949, dan menimbulkan kerugian ekonomi yang sangat besar (Thomas dan Mare 1945; Von Backstrom, 1945; Diesel, 1949). Pada tahun 1957, LSD diidentifikasi di Afrika Timur di Kenya. Pada tahun 1972, penyakit ini dilaporkan di Sudan (Ali dan Obeid 1977) dan Afrika Barat pada tahun 1974. Sementara itu menyebar ke Somalia pada tahun 1983 (Davies 1991 a dan b).

Penyakit ini terus menyebar ke sebagian besar benua Afrika dalam serangkaian epizootik seperti yang dicatat sebelumnya oleh Davies (1991 b) dan House (1990). Pada tahun 2001, LSD dilaporkan di Mauritius, Mozambik dan Senegal.

Saat ini, LSD terjadi di sebagian besar benua Afrika (kecuali Libya, Aljazair, Maroko dan Tunisia) (Tuppurainen dan Oura 2012). Hingga tahun 1980-an (Dari 1929 hingga 1984) penyakit ini terbatas pada negara-negara di benua Afrika Sub-Sahara, meskipun kemungkinan untuk bergerak melampaui kisaran ini telah diusulkan (Davies 1981).

Di Timur Tengah, wabah LSD dilaporkan di Oman pada tahun 1984 dan 2009 (Houseet al1990; Kumar 2011; Tageldin 2014). Kuwait pada tahun 1986 dan 1991, Mesir pada tahun 1988 dan 2006 (Aliet al1990; Rumahet al1990; Davies 1991a; Fayez dan Ahmed 2011; Ali dan Amina 2013), Israel pada 1989 dan 2006 (Shimshony 1989; APHIS 2006; Shimshony dan Economides 2006), Bahrain pada 1993 dan 2002-2003, Yaman, Uni Emirat Arab pada 2000 dan Tepi Barat juga melaporkan invasi LSD (Shimshony dan Economides, 2006; Kumar 2011; Sherrylinet al 2013). Di Oman, LSD muncul kembali pada tahun 2009 pada populasi peternakan 3200 hewan Holstein dengan 9 tingkat morbiditas dan mortalitas tinggi masing-masing 30-45% dan 12% (Tageldinet al2014). Di Mesir, Kegubernuran Suez, LSD dilaporkan pada Mei 1988 (Aliet al 1990). Penyakit itu tiba di Mesir dengan ternak yang diimpor dari Afrika dan disimpan di stasiun karantina setempat. Ini menyebar secara lokal pada musim panas 1988 dan tampaknya melewati musim dingin dengan sedikit atau tanpa manifestasi penyakit klinis. Dua puluh dua dari dua puluh enam gubernuran Mesir terkena penyakit, kemudian penyakit itu muncul kembali pada musim panas 1989 dan berlanjut selama lima sampai enam bulan. Epizootik ini menunjukkan tingkat morbiditas yang rendah (2%) karena prosedur vaksinasi yang mencakup hampir dua juta sapi dengan vaksin cacar domba. Namun, sekitar 1449 hewan mati. Pada musim panas 2006, di satu peternakan dengan total 30 kasus pada sapi perah. Wabah LSD muncul kembali di beberapa gubernuran Mesir, di mana semua kelompok umur dan jenis kelamin ternak Mesir terinfeksi dengan komplikasi yang parah dan serius. (Fayez dan Ahmed 2011; Ali dan Amina 2013). Di Israel, LSD dilaporkan pada tahun 1989. Wabah ini terjadi

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kemudian dibuang dengan penyembelihan semua ternak yang terinfeksi serta kontak. Selain itu, vaksinasi cincin dengan galur cacar domba dilakukan di sekitar area fokus yang membatasi penyebaran penyakit.

Salah satu wabah LSD baru-baru ini di benua Afrika terjadi di Ethiopia tengah pada tahun 2007 hingga 2011. Wabah ini digambarkan aktif. Itu diselidiki di empat distrik: Adama, Wenji, Mojo dan Welenchiti. Total 1.675 wabah dilaporkan selama periode 5 tahun dari 2007 hingga 2011, dengan 62.176 kasus dan 4.372 kematian. Oromia mewakili jumlah wabah tertinggi (1.066), diikuti oleh Amhara (365) dan Bangsa Selatan, Kebangsaan dan Wilayah Rakyat (123). Tahun 2010 dilaporkan jumlah wabah tertinggi yang sering terlihat antara bulan September dan Desember. Angka kesakitan dan kematian masing-masing adalah 13,61% (296) dan 4,97% (Ayeletet al2014).

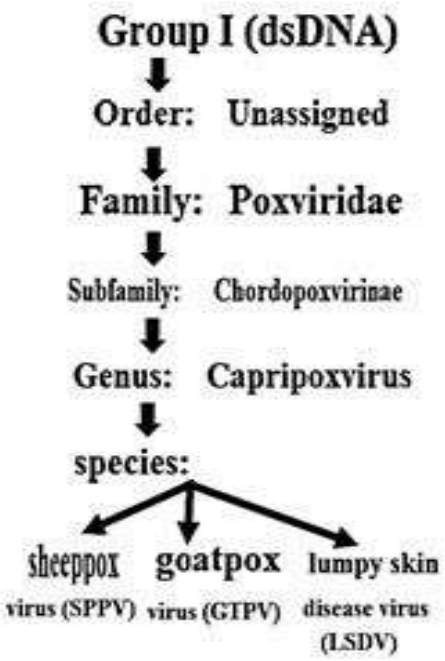
Suriah, Lebanon, dan Yordania bergabung dengan negara-negara yang terkena LSD pada tahun 2012 dan 2013. Penyakit ini telah dilaporkan di Turki pada bulan Oktober 2013, Iran dan Irak pada tahun 2014 (Gambar 2) (Sherrylinet al2013; *Lumpy Skin Disease*, Irak 2015).

Di Yordania, LSD dilaporkan sebagai penyakit baru. Wabah dimulai pada pertengahan April 2013. Dua sapi perah dewasa di distrik Bani Kenanah, Kegubernuran Irbid, di perbatasan Yordania Israel dan Suriah, menunjukkan tanda-tanda klinis yang menunjukkan LSD dan dipastikan positif oleh PCR. Tingkat morbiditas keseluruhan adalah 26%, tingkat kematian 1,9% dan tingkat fatalitas kasus 7,5% (Abutarbushet al2013).

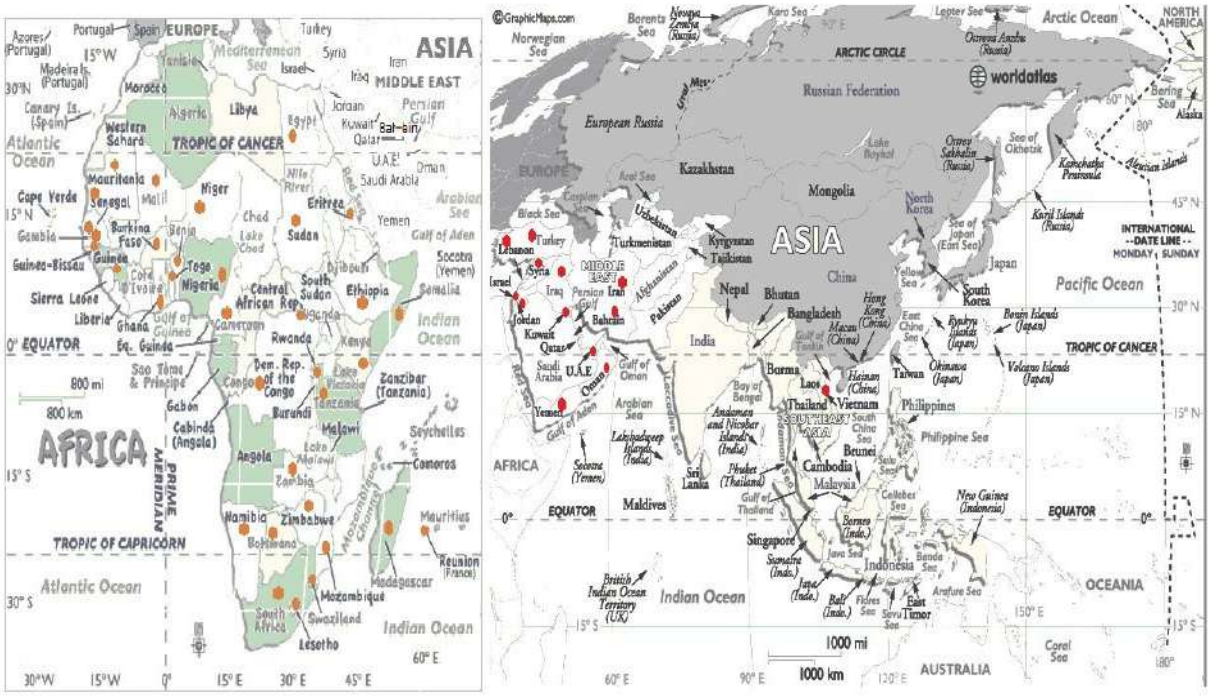
Di Iran, LSD dianggap sebagai penyakit baru yang diidentifikasi pertama kali pada tahun 2014. Secara total, enam kasus dilaporkan pada sapi perah. Wabah dilaporkan di dua desa di bagian barat negara itu. Pergerakan hewan secara ilegal dan vektor biasa dianggap sebagai sumber wabah. (Situs ternak 2014). Harapan perjalanan dan invasi LSD ke negara-negara tetangga yang bebas adalah mungkin. LSD dapat menyerang utara dan barat dari Turki ke Eropa dan Kaukasus dan dari Timur ke Asia Tengah dan Selatan. Selain itu, Federasi Rusia di utara dan Bulgaria serta Yunani di barat dianggap sebagai negara berisiko.

Gambar 1. Klasifikasi virus penyakit kulit Lumpy

MRVSA 3(3), 6-23. Al Shalihi 2014
http://mirrorofresearchinveterinarysciencesandanimals.com/
ISSN 2307-8073



Gambar 2. Peta Sebaran Penyakit Kulit Benjolan (Titik merah menunjukkan munculnya fokus penyakit)



Epidemiologi

A. Angka kesakitan dan kematian

MRVSA 3(3), 6-23. Al Shalihi 2014
http://mirrorofresearchinveterinarysciencesandanimals.com/
ISSN 2307-8073

Ada variasi besar dalam tingkat morbiditas dan mortalitas wabah LSD. Itu tergantung pada faktor-faktor ini: lokasi geografis dan iklim; kondisi manajemen; status gizi dan kondisi umum hewan; jenis ternak yang terkena dampak; status kekebalan; tingkat populasi dan penyebaran vektor serangga diduga di berbagai habitat; virulensi virus. Tingkat morbiditas LSD berkisar antara 5 hingga 45%. Namun, tingkat morbiditas 1 hingga 5 persen dianggap lebih umum. Tingkat yang lebih tinggi telah ditemukan pada epizootik di Afrika Selatan, Barat dan Timur dan Sudan meskipun sejauh ini tingkat yang jauh lebih rendah dapat terjadi selama epizootik yang sama. Selain itu, tingkat morbiditas dan mortalitas yang tinggi masing-masing 30-45% dan 12% juga dilaporkan di Oman pada tahun 2009 pada populasi peternakan sapi Holstein (Sherrylinet al2013).

B. Hewan yang rentan

LSD memiliki kisaran inang vertebrata yang sempit. Sapi dan Kerbau adalah spesies yang terinfeksi secara alami selama wabah di lapangan. Lima kejadian kasus klinis LSD pada Bubalus bubalis, kerbau Asia telah dilaporkan (Aliet al1990). Tidak ada spesies ruminansia domestik lain yang terinfeksi secara alami selama wabah di lapangan. Semua breed ternak tampaknya sama-sama rentan terhadap penyakit ini. Akan tetapi, beberapa peneliti lain menemukan bahwa breed impor dengan kulit tipis, seperti sapi Bos taurus, sapi Friesland dan Channel Island, jauh lebih rentan daripada breed asli dengan kulit lebih tebal, seperti breed silangan Afrikaner dan Afrikaner. Pedet muda lebih rentan terhadap penyakit ini dan dapat mengembangkan lesi yang khas dalam waktu 24 hingga 48 jam, meskipun semua kelompok umur hewan rentan. Satu kasus klinis infeksi Capripox, mungkin LSD, dijelaskan pada oryx Arab di kebun binatang di Arab Saudi. (Grethet al1992). Inokulasi eksperimental beberapa spesies liar seperti: impala (Aepyceros melampus), Thomsons gazelle (Gazella thomsonii) dan jerapah (Giraffa camelopardalis), diikuti dengan perkembangan lesi LSD di kulit (Younget al1968).

C. Transmisi

Penularan virus *Lumpy Skin Disease* belum sepenuhnya dipahami (Weiss 1968; Kitching dan Mellor 1986; Carn dan Kitching 1995). Penyebaran mekanis virus LSD terutama terkait dengan serangga terbang dan semua petunjuk yang mungkin menegaskan pengamatan lapangan bahwa epidemi LSD terjadi pada periode aktivitas serangga penggigit terbesar. Sebagian besar kasus diyakini disebabkan oleh penularan oleh vektor arthropoda. Terdapat variasi tingkat serangan dari 10-15% hingga hampir 100% pada epidemi yang berbeda karena perbedaan spesies vektor aktif yang ditemukan pada situasi yang berbeda. Stomoxys, tabanids dan lalat tsetse, cenderung diragukan dalam kondisi kering dan terkait dengan tingkat penularan yang lebih rendah. Namun, tempat perkembangbiakan nyamuk yang besar sering terjadi pada tingkat morbiditas yang sangat tinggi yang terjadi setelah hujan.
Lubinga (2014), telah ditemukan tiga spesies kutu keras pengisap darah, yang terlibat dalam penularan LSDV di Afrika sub-Sahara. Tiga spesies kutu yang diidentifikasi sebagai vektor penyakit adalah Rhipicephalus (Boophilus) decoloratus (kutu biru), R. appendiculatus (kutu telinga coklat) dan Amblyomma hebraeum (kutu bont). Studi Lubinga telah mengkonfirmasi bahwa kutu bertindak sebagai vektor virus. Lubinga menyatakan: "Kutu juga bertindak sebagai 'reservoir' untuk virus, karena dapat bertahan dalam parasit eksternal ini selama periode antara epidemi. "Virus telah ditemukan dalam air liur dan organ serta

MRVSA 3(3), 6-23. Al Shalihi 2014
http://mirrorofresearchinveterinarysciencesandanimals.com/
ISSN 2307-8073

berpotensi menahan musim dingin di kutu ini. Lubinga menyebutkan bahwa kutu dapat menyebar dalam jarak jauh dengan bergerak bersama hewan inangnya, misalnya saat memakan burung yang bermigrasi, dan perubahan iklim akibat pemanasan global memungkinkan kutu untuk bertahan hidup dengan sukses dan mencari di daerah di mana sebelumnya mereka tidak dapat bertahan karena kondisi yang sangat dingin. Bukti yang sama telah diterbitkan dan melaporkan kemungkinan peran kutu keras dalam transmisi LSDV (Tuppurainen et al., 2011). Studi ini menunjukkan bukti molekuler transmisi LSDV transstadial dan transovarial oleh kutu Rhipicephalus (Boophilus) decoloratus, dan transmisi mekanis atau intrastadial oleh kutu Rhipicephalus appendiculatus dan Amblyomma hebraeum.

Virus LSD telah diisolasi dari Stomoxys calcitrans dan Musca confiscata dan ditransmisikan secara eksperimental menggunakan S. calcitrans tetapi vektor lain juga diragukan termasuk Biomyia, Culicoides, Glossina dan Musca spp. Namun, dalam penelitian baru-baru ini, meskipun terdeteksi virus pada nyamuk (Anopheles stephensi, Culex quinquefascuatus) lalat kandang dan nyamuk penggigit (Culicoides nebeculosis) setelah mereka memberi makan sapi dengan *Lumpy Skin Disease*, infeksi tidak menular ke orang yang rentan. ternak ketika arthropoda ini diizinkan untuk memakannya kembali.

Sapi dapat terinfeksi melalui air minum, meskipun konsumsi dan penularan kontak langsung bukan rute yang umum, meskipun virus terdapat dalam sekret hidung dan lakrimal, air mani, dan susu hewan yang terinfeksi. Penularan LSDV melalui semen (perkawinan alami atau inseminasi buatan) belum pernah dibuktikan secara eksperimental, tetapi LSDV telah diisolasi dalam semen sapi jantan yang terinfeksi secara eksperimental.

Infeksi intra-uterus diasumsikan, yang didukung oleh adanya lesi kulit yang luas pada pedet yang diaborsi (Weiss 1968; Ironset al2005). Beberapa spesies liar (jerapah, impala, dan rusa Thomson) telah terinfeksi oleh inokulasi parenteral dengan virus LSD dan telah mengembangkan lesi yang khas. Lesi LSD belum terlihat pada hewan ini, ketika mereka hadir selama epizootik penyakit. Domba dan kambing tidak terinfeksi selama wabah LSD bahkan ketika berada dalam kontak dekat dengan ternak yang terinfeksi. Kerbau Afrika (Syncerus caffer) tidak menunjukkan lesi di lapangan selama epizootik LSD, dan mayoritas kerbau Asia, Bubalus bubalis, juga tidak terpapar selama epizootik LSD Mesir. Lima kasus lesi mirip LSD pada kerbau dilaporkan di Mesir. Kedua jenis kerbau tersebut dapat menderita infeksi yang tidak terlihat dan seroconvert. Sementara infeksi melalui kontak dapat terjadi, ini diperkirakan terjadi hanya pada tingkat yang rendah dan tidak dianggap sebagai komponen utama penularan selama epizootik. Perpindahan hewan dari ternak yang terinfeksi, seringkali berbulan-bulan setelah pemulihan, secara teratur mengakibatkan masuknya infeksi. Sumber virus dianggap dari lesi kulit lama. Di sebagian besar Afrika Sub-Sahara, penyakit ini diamati muncul setelah hujan musiman. Selalu ada peningkatan populasi spesies arthropoda yang berbeda. Pergerakan lokal penyakit di hadapan karantina yang ketat telah dikaitkan dengan pergerakan udara vektor serangga dalam aliran udara tingkat rendah. Timbulnya embun beku di Afrika Selatan dan Mesir menghasilkan penurunan besar dalam jumlah kasus LSD, yang hampir menghilang selama musim dingin untuk muncul kembali di musim semi dan musim panas. Penyakit ini menyebar ke seluruh Mesir pada musim panas 1989, meskipun ada pembatasan total pada pergerakan hewan. Fokus LSD muncul di Israel sekitar 80-200 km jauhnya dari fokus aktif transmisi LSD di Mesir, ini menunjukkan bahwa telah terjadi pergerakan udara dari serangga penggigit. Pemberlakuan karantina memang mencegah penyebaran infeksi oleh hewan yang pulih tetapi tidak dengan pergerakan vektor melalui udara (Fayez dan Ahmed 2011).

MRVSA 3(3), 6-23. Al Shalihi 2014
http://mirrorofresearchinveterinarysciencesandanimals.com/
ISSN 2307-8073

Kontak langsung dianggap sebagai cara penularan yang tidak efektif. Titik penggembalaan dan penyiraman ternak komunal telah dikaitkan dengan terjadinya LSD. Penularan LSDV melalui semen (perkawinan alami atau inseminasi buatan) belum dibuktikan secara eksperimental, tetapi LSDV telah diisolasi dalam semen sapi jantan yang terinfeksi secara eksperimental (Weiss 1968; Ironset al2005).

Patogenesis

Rute intravena, intradermal dan subkutan digunakan dalam infeksi eksperimental. Rute intravena mengembangkan infeksi umum yang parah, sedangkan inokulasi intraepidermal berkembang hanya 40% sampai 50% hewan dapat mengembangkan lesi lokal atau tidak ada penyakit sama sekali. Pembengkakan lokal di tempat inokulasi setelah empat sampai tujuh hari dan pembesaran kelenjar getah bening regional, berkembang setelah inokulasi subkutan atau intradermal sapi dengan LSDV (Vorster dan Mapham 2008). Namun, erupsi nodul kulit yang umum biasanya terjadi tujuh hingga 19 hari setelah inokulasi. LSDV bereplikasi di dalam sel inang seperti makrofag, fibroblas, pericytes dan sel endotel di limfatik dan dinding pembuluh darah menyebabkan berkembangnya vaskulitis dan limfangitis, sedangkan trombosis dan infark dapat berkembang pada kasus yang parah. Viraemia terjadi setelah reaksi demam awal dan bertahan selama dua minggu. Pada infeksi alami, pedet yang masih sangat muda, sapi laktasi, dan hewan yang kekurangan gizi tampaknya mengembangkan penyakit yang lebih parah yang mungkin disebabkan oleh gangguan imunitas humoral. Kekebalan yang diperantarai sel seumur hidup dikembangkan pada sebagian besar hewan yang sembuh dari penyakit klinis. Pedet yang lahir dari sapi yang terinfeksi memperoleh antibodi ibu yang dapat melindungi mereka dari penyakit klinis selama kurang lebih enam bulan. LSDV ditunjukkan dalam air liur setidaknya selama 11 hari setelah berkembangnya demam, dalam air mani selama 42 hari dan dalam nodul kulit selama 39 hari, dari ternak yang terinfeksi secara eksperimental. dan hewan yang kekurangan gizi tampaknya mengembangkan penyakit yang lebih parah yang mungkin disebabkan oleh gangguan imunitas humoral. Kekebalan yang diperantarai sel seumur hidup dikembangkan pada sebagian besar hewan yang pulih dari penyakit klinis. Pedet yang lahir dari sapi yang terinfeksi memperoleh antibodi ibu yang dapat melindungi mereka dari penyakit klinis selama kurang lebih enam bulan. LSDV ditunjukkan dalam air liur setidaknya selama 11 hari setelah berkembangnya demam, dalam air mani selama 42 hari dan dalam nodul kulit selama 39 hari, dari ternak yang terinfeksi secara eksperimental. dan hewan yang kekurangan gizi tampaknya mengembangkan penyakit yang lebih parah yang mungkin disebabkan oleh gangguan imunitas humoral. Kekebalan yang diperantarai sel seumur hidup dikembangkan pada sebagian besar hewan yang pulih dari penyakit klinis. Pedet yang lahir dari sapi yang terinfeksi memperoleh antibodi ibu yang dapat melindungi mereka dari penyakit klinis selama kurang lebih enam bulan. LSDV ditunjukkan dalam air liur setidaknya selama 11 hari setelah berkembangnya demam, dalam air mani selama 42 hari dan dalam nodul kulit selama 39 hari, dari ternak yang terinfeksi secara eksperimental.

Tanda-tanda klinis

Gejala klinis LSD memiliki dua fase demam (biphasic fever), yang muncul setelah varian masa inkubasi 4-12 hari (biasanya 7 hari). Suhu hewan yang terinfeksi meningkat menjadi 40-41,5°C, yang dapat bertahan selama 6-72 jam atau lebih dan jarang sampai 10 hari. Hewan yang terinfeksi juga menunjukkan lakrimasi, peningkatan sekresi hidung dan faring, anoreksia, disgalaktia, depresi umum dan keengganan untuk bergerak. Tanda-tanda klinis awal LSD bervariasi dalam tingkat keparahan yang bergantung pada sistem pengelolaan kawanan tetapi tidak berhubungan dengan jenis kelamin atau usia hewan.
Beberapa nodul berbatas tegas berkembang di kulit hewan. Bintil ini tiba-tiba meletus dalam 1-2 hari. Nodul yang erupsi dapat tersebar luas atau terbatas pada beberapa lesi saja. Kepala, leher, perineum, genitalia, ambing, dan ekstremitas merupakan tempat predileksi. Seluruh kulit hewan yang terinfeksi ditutupi dengan lesi, jarang terjadi. Lesi LSD tipikal berbentuk bulat, tidak beraturan, berdiameter sekitar 5-50 mm, dan tampak sebagai area berbatas tegas dari rambut tegak di atas area kulit yang keras dan sedikit terangkat (Gambar 3). Kulit yang sehat jelas dikenali dari reaksi kulit yang berdekatan. Kulit yang terkena hiperemik, dan mungkin ada butiran serum yang keluar darinya. Lesi setebal kulit penuh dan melibatkan epidermis, dermis dan sub-kutis, seringkali dengan beberapa edema. Mereka perlahan mengeras dan membentuk lekukan (lesung pipit) di tengahnya. Kelenjar getah bening regional mudah teraba dan membesar hingga 3-5 kali ukuran normal. Beberapa massa (benjolan) dapat dideteksi di subkutan

MRVSA 3(3), 6-23. Al Shalihi 2014
http://mirrorofresearchinveterinarysciencesandanimals.com/
ISSN 2307-8073

jaringan dan sering didistribusikan ke seluruh jaringan ikat dan otot dalam tubuh (Diesel 1949). Lesi penyakit juga berkembang pada moncong di nares dan orofaring. Moncongnya menunjukkan lesi seperti cincin yang khas karena pengelupasan lesi nekrotik dari epitel sekitarnya yang sehat. Laring, trakea, saluran pencernaan terutama abomasum juga dapat mengembangkan lesi (nekrosis dan ulserasi) yang menyebabkan gastro-enteritis parah. Keratitis adalah komplikasi umum. Discharge mukopurulen muncul dari nares, menetes terus-menerus dari mulut, batuk dan pernapasan sering sesak napas, jika laring dan trakea yang terlibat (Ayre-Smith 1960).

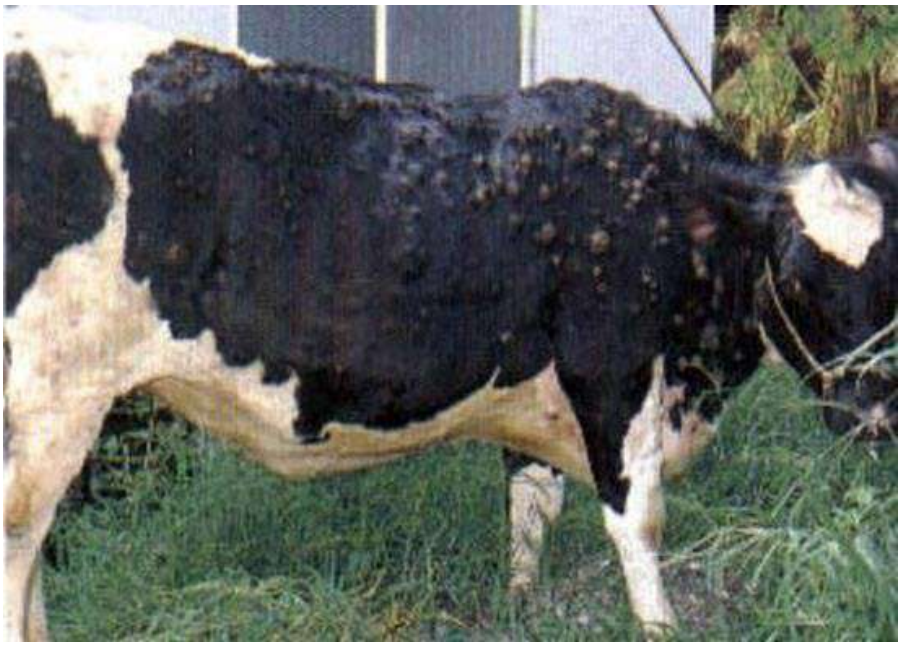
Setelah 2-3 minggu, lesi kulit secara bertahap menjadi lebih keras dan nekrotik. Beberapa lesi yang terkait dengan pembentukan plak edema yang keras, menyebabkan rasa tidak nyaman dan nyeri yang parah serta menghambat pergerakan. Kemudian, "sitfast" LSD dikembangkan dari lesi yang lebih keras (inti jaringan nekrotik membentuk sumbat). Ada cincin berbeda dari jaringan hidup di sekitar lesi. Beberapa "sitfast" dapat terkelupas, meninggalkan lubang setebal kulit penuh di kulit, yang sembuh dengan granulasi. Bakteri dapat menyerang lubang. Tungkai membengkak beberapa kali ukuran normalnya karena peradangan, edema, dan area nekrotik yang luas kulit yang keras di atas tungkai yang mengalami edema kronis dapat terkelupas, meninggalkan area luas yang dapat terinfeksi atau rentan terhadap myasis. Ini menjadi perhatian utama, ketika Cochliomyia homnivorax terjadi di Afrika Utara.

Sekuel umum dari LSD adalah pneumonia, terkait dengan area besar konsolidasi abu-abu berukuran 20-30 mm, yang bisa berakibat fatal. Menghirup jaringan nekrotik dari lesi yang lebih tinggi di saluran pernapasan telah terbukti berakibat fatal, beberapa bulan setelah infeksi awal. Aborsi adalah sekuel umum dari fase akut penyakit; janin yang diaborsi dan anak sapi hidup telah diamati dengan lesi kulit LSD. Infertilitas adalah masalah setelah infeksi LSD; betina tetap anestrus selama beberapa bulan dan sebagian besar sapi yang terinfeksi menderita penghentian aktivitas ovarium terutama karena kondisi tubuh yang buruk. Sapi jantan yang terinfeksi, yang menderita luka pada alat kelamin, mungkin juga mandul selama berbulan-bulan.

Lesi pernapasan, mulut, faring, dan okular memperpanjang periode anoreksia dan pemulihan. Penurunan kondisi umum terjadi pada hewan yang terkena dampak parah dan dalam kondisi kisaran kematian bisa tinggi. Hewan yang pulih menderita kelemahan dan kelemahan hingga 6 bulan. Sebagian besar hewan yang terkena dampak mengembangkan nodul yang relatif sedikit dan pulih dengan lancar. Akan tetapi, LSD merupakan penyakit serius yang mempengaruhi produksi, walaupun proporsi hewan yang mengalami komplikasi kronis mungkin rendah; kurang dari 5% dari mereka yang terkena dampak (Gezahegnet al2013).

Gambar 3. Sapi yang terinfeksi LSD menunjukkan banyak nodul kulit (dari wabah Irak baru-baru ini)

MRVSA 3(3), 6-23. Al Shalihi 2014
http://mirrorofresearchinveterinarysciencesandanimals.com/
ISSN 2307-8073



Patologi

1. Temuan patologis yang parah

LSD memiliki lesi kotor yang dijelaskan dengan baik. Nodul kulit biasanya berukuran seragam, bulat dan menonjol, tetapi beberapa mungkin menyatu menjadi plak besar yang tidak beraturan dan berbatas tegas. Permukaan potongan nodul berwarna abu-abu kemerahan, selain itu, akumulasi cairan serosa abu-abu kemerahan dan edema di lapisan subkutis. Lesi yang sembuh muncul sebagai indurasi yang disebut "sitfasts" atau menyendiri atau dapat membentuk ulkus yang dalam. Lesi pencernaan nekrotik melingkar yang khas juga dapat dilihat pada moncong, rongga hidung, laring, trakea, bronkus, bagian dalam bibir, gingiva, bantalan gigi, ulu hati, abomasum, rahim, vagina, puting susu, ambing dan testis (Aliet al1990). Kelenjar getah bening regional membesar secara nyata dan dapat menjadi 3-5 kali ukuran biasanya, edema dan memiliki fokus piemik, selain selulitis lokal. Jaringan otot dan fascia di atas otot tungkai dapat menunjukkan lesi nodular yang berwarna putih keabu-abuan yang dikelilingi oleh jaringan inflamasi berwarna merah. Nodul yang sama didistribusikan ke seluruh bangkai. Diameternya sekitar 10-30 mm di ginjal. Interstisial atau bronkopneumonia yang berhubungan dengan lesi berdiameter 10-20 mm juga tersebar di paru-paru. Lesi ini dihasilkan dari infiltrasi 'celles claveleuses' epiteloid besar, dijelaskan oleh Borrel untuk cacar domba. Lesi dipisahkan dari epitel nekrotik jauh dari jaringan sehat. Jaringan nekrotik mengelupas meninggalkan ulkus yang perlahan sembuh dengan granulasi.et al1971; El-Neweshyet al2012; Kumar 2011).

2. Temuan histopatologis

Temuan histopatologi penyakit LSD sangat khas dan memberikan dasar untuk diagnosis. Lesi sangat bervariasi tergantung pada stadiumnya

MRVSA 3(3), 6-23. Al Shalihi 2014
http://mirrorofresearchinveterinarysciencesandanimals.com/
ISSN 2307-8073

perkembangan. Pada stadium akut penyakit, sebagian besar ditandai dengan lesi vaskulitis, trombosis, infark, fibroplasia perivaskular. Sel inflamasi menyusup ke area yang terinfeksi, yang meliputi makrofag, limfosit, dan eosinofil. Keratinosit, makrofag, sel endotel, dan perisit dapat terlihat inklusi eosinofilik intrasitoplasma. Lapisan epidermis dan dermis dari hewan yang terinfeksi menunjukkan edema dan disusupi dengan sel tipe makrofag epiteloid besar.

Ada edema dan infiltrasi epidermis dan dermis dengan sel tipe makrofag epiteloid besar, yang juga telah dideskripsikan dengan baik untuk cacar domba. Mereka ditemukan dengan sel plasma dan limfosit pada lesi awal, dan pada lesi yang lebih tua, fibroblas dan leukosit polimorfonuklear dengan beberapa sel darah merah mendominasi. Proliferasi endotel terlihat pada pembuluh darah dermis dan subkutis, dengan limfositik memborgol pembuluh darah, yang menyebabkan trombosis dan nekrosis. Inklusi intrasitoplasma spesifik dapat ditemukan di berbagai elemen epitel, kelenjar sebaceous, dan epitel folikel. Ini sebagian besar eosinofilik-ungu dan tampaknya memiliki halo yang jelas di sekitarnya, yang mungkin merupakan artefak pemrosesan. Lesi pada dasarnya sama di seluruh tubuh (Burdin 1959; Aliet al1990; El-Neweshyet al2012; Ali dan Aminah 2013).

Diagnosa

Diagnosis LSD didasarkan pada tanda-tanda klinis yang khas dikombinasikan dengan konfirmasi laboratorium adanya virus atau antigen (Gambar 4).

1.Diagnosis dugaan LSD di lapangan dapat didasarkan pada:

A. Morbiditas, mortalitas dan tanda klinis yang mencerminkan LSD seperti:

1. Penyakit menular dengan bintil kulit yang menyeluruh
2. Karakteristik nekrosis kerucut terbalik pada nodul kulit (sitfast), Pembesaran kelenjar getah bening yang mengeringkan area yang terkena.
3. Demam terus-menerus, kurus, dan kematian rendah.
4. Lesi cacar pada selaput lendir mulut, faring, epiglotis, lidah dan seluruh saluran pencernaan, selaput lendir rongga hidung, trakea dan paru-paru 6. Edema dan area atelektasis lobular fokal di paru-paru
7. Pleuritis dengan pembesaran kelenjar getah bening mediastinum pada kasus yang parah
8. Sinovitis dan tendosinovitis dengan fibrin pada cairan sinovial
9. Lesi cacar mungkin ada di testis dan kandung kemih

B. Gambaran histopatologis

Biopsi kulit dari lesi awal cocok untuk histopatologi dan harus diawetkan dalam formalin buffer 10 persen. Fitur histopatologi yang paling diagnostik adalah:
1. Kemacetan, perdarahan, edema, vaskulitis, dan nekrosis selalu dikaitkan dengan nodul yang melibatkan semua lapisan kulit, jaringan subkutan, dan otot yang berdekatan.
2. Proliferasi limfoid, edema, kongesti dan perdarahan.
3. Vaskulitis, trombosis, infark, fibroplasia perivaskular, dan infiltrasi seluler

MRVSA 3(3), 6-23. Al Shalihi 2014
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4. Inklusi eosinofilik intrasitoplasma dapat terlihat pada sel yang berbeda.

3. Diagnosis konfirmasi LSD dapat didasarkan pada:

- **Investigasi laboratorium dan identifikasi agen berdasarkan**(Manual Terestrial OIE 2010; OIE 2013):

A. Isolasi virus

Konfirmasi *Lumpy Skin Disease* di daerah baru memerlukan isolasi dan identifikasi virus. Sampel untuk isolasi virus harus dikumpulkan dalam minggu pertama munculnya tanda-tanda klinis, sebelum pengembangan antibodi penawar (Davies 1991; Davieset al1971). Biopsi kulit dari lesi awal (yang belum terjadi nekrosis) memberikan sampel yang dapat digunakan untuk isolasi virus dan mikroskop elektron. Selain itu, virus LSD dapat diisolasi dari buffy coat dari sampel darah yang dikumpulkan ke dalam EDTA atau heparin selama tahap viraemic LSD. Sampel harus diambil dari setidaknya tiga hewan. Sampel yang disedot dari kelenjar getah bening yang membesar juga dapat digunakan untuk isolasi virus. Virus LSD tumbuh dalam kultur jaringan yang berasal dari bovine, ovine atau caprine. Sel dermis sapi atau sel lamb testis (LT) (Kultur primer atau sekunder), dianggap sebagai sel yang paling rentan. Capripoxvirus LSD juga telah diadaptasi untuk tumbuh pada membran chorioallantoic telur ayam berembrio dan sel ginjal monyet hijau Afrika (Vero), yang tidak direkomendasikan untuk isolasi primer (OIE Terrestrial Manual 2010).

B. Mikroskop elektron

Diagnosis transmisi elektron mikroskopis (TEM) LSD dapat dikonfirmasikan dalam beberapa jam setelah penerimaan spesimen. Demonstrasi TEM virus dalam sediaan spesimen biopsi yang diwarnai negatif yang diambil dari kulit atau selaput lendir yang terkena. Virion capripox dewasa memiliki ukuran rata-rata 320 x 260 nm dan memiliki profil yang lebih oval dan badan lateral yang lebih besar daripada virion orthopox (OIE Terrestrial Manual 2010).

C. Tes antibodi fluoresen

Antigen capripoxvirus juga dapat diidentifikasi pada kaca penutup yang terinfeksi atau slide kultur jaringan menggunakan tes antibodi fluoresen.

D. Imunodifusi gel agar

Tes agar gel immunodiffusion (AGID) telah digunakan untuk mendeteksi antigen pencetus capripoxvirus, tetapi memiliki kelemahan bahwa antigen ini digunakan bersama oleh parapoxvirus.

E. Uji imunosorben terkait-enzim

Itu dibuat dengan menggunakan antigen rekombinan yang diekspresikan untuk menghasilkan antiserum poliklonal monospesifik P32 dan produksi antibodi monoklonal (MAbs) (Carn,et al 1994).

MRVSA 3(3), 6-23. Al Shalihi 2014
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ISSN 2307-8073

F.**Reaksi berantai polimerase (PCR)**dan pengujian loop-mediated isothermal amplification (LAMP) telah digunakan untuk mendeteksi capripoxvirus dengan sensitivitas yang lebih tinggi. (Bowdenet al2009; Balinskyet al2008).

• Serologi

Sera beku dari hewan akut dan penyembuhan digunakan. Netralisasi virus (reaksi silang dengan semua capripoxvirus) dan tes antibodi fluoresen tidak langsung (reaksi silang dengan parapoxvirus) umumnya digunakan. Uji imunosorben terkait-enzim untuk mendeteksi antibodi terhadap virus capripox telah dikembangkan menggunakan protein struktural P32 yang diekspresikan (Carnet al., 1994; Heineet al1999). Tes imunodifusi agar gel (Tes ini dapat memberikan reaksi positif palsu karena reaksi silang dengan virus stomatitis papular bovine dan virus pseudocowpox). Analisis western blot menyediakan sistem yang sensitif dan spesifik untuk mendeteksi antibodi terhadap protein struktural capripoxvirus, walaupun tesnya mahal dan sulit dilakukan.

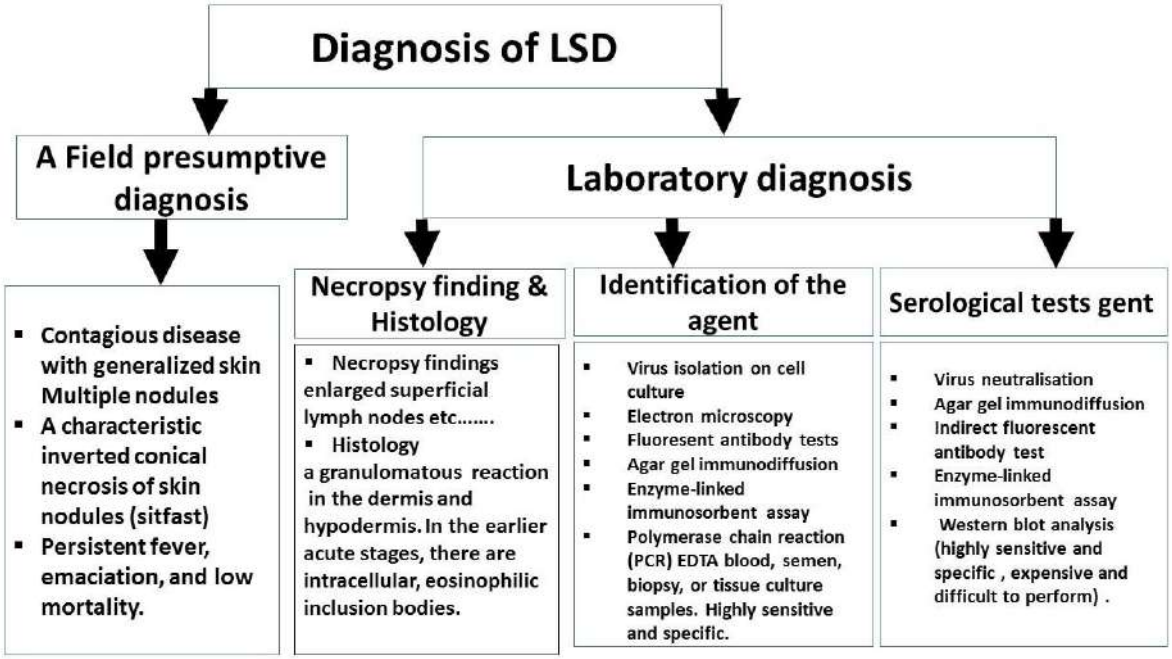
Perbedaan diagnosa

Ada banyak penyakit yang menyebabkan gejala serupa dari LSD. Penting untuk mendapatkan diagnosis yang pasti untuk memastikan tindakan pencegahan dan pengendalian terbaik untuk ternak yang rentan. LSD dapat dikacaukan dengan penyakit berikut:

- Penyakit kulit semu
- Diare virus sapi/penyakit mukosa
- Demodikosis (Demodex)
- Demam catarrhal ganas sapi (Snotsiekte)
- Rinderpest
- Besnoitiosis
- Onkoserkariasis
- Alergi gigitan serangga

Gambar 4. Prosedur diagnostik LSD

MRVSA 3(3), 6-23. Al Shalihi 2014
http://mirrorofresearchinveterinarysciencesandanimals.com/
ISSN 2307-8073



Perlakuan

Penyakit kulit yang menggumpal disebabkan oleh virus dan oleh karena itu belum diketahui obatnya. Namun, antibiotik, obat antiinflamasi atau suntikan vitamin digunakan dalam beberapa kasus untuk mengobati infeksi bakteri sekunder atau untuk mengatasi demam atau peradangan dan peningkatan nafsu makan hewan.

Kontrol

Pengendalian penyakit kulit Lumpy dengan karantina dan kontrol pergerakan tidak terlalu efektif karena lalat penggigit dan spesies kutu tertentu kemungkinan besar merupakan metode penularan penyakit yang paling penting. Meskipun pengendalian serangga tidak efektif dalam mencegah penyebaran LSD, namun penggunaan insektisida bersama dengan repelan dapat membantu pencegahan penyebaran LSD. Wabah LSD dapat diberantas dengan karantina, depopulasi hewan yang terinfeksi dan terpapar, pembuangan bangkai yang tepat, pembersihan dan disinfeksi tempat dan pengendalian serangga.

Pengendalian LSD hanya dapat dilakukan dengan vaksinasi atau imunoprofilaksis. Vaksin hidup membantu mengendalikan kerugian akibat *Lumpy Skin Disease* di daerah endemik. Menurut OIE, empat strain capripoxvirus hidup yang dilemahkan telah digunakan sebagai vaksin khusus untuk pengendalian LSD (Brenneret al, 2006; Capstick & Coakley 1961 & 1962; Carnet al., 1994). Ini adalah: galur virus cacar domba dan kambing Kenya yang ditularkan 18 kali dalam sel testis domba (LT) atau sel otot betis janin, galur cacar domba Yugoslavia RM 65, galur cacar domba Rumania dan galur virus *Lumpy Skin Disease* dari Afrika Selatan, yang ditularkan 60 kali pada sel ginjal domba dan 20 kali pada membran chorioallantoic telur ayam berembrio.

Vaksin berikut telah digunakan untuk melindungi hewan:

MRVSA 3(3), 6-23. Al Shalihi 2014
http://mirrorofresearchinveterinarysciencesandanimals.com/
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- Vaksin virus hidup yang dilemahkan homolog (strain Neethling: kekebalan yang diberikan bertahan hingga 3 tahun).
- Vaksin virus hidup yang dilemahkan heterolog (Vaksin cacar domba atau kambing, tetapi dapat menyebabkan reaksi lokal, terkadang parah). Vaksin ini tidak disarankan di negara-negara yang bebas dari cacar domba dan kambing karena vaksin hidup dapat menjadi sumber infeksi bagi populasi domba dan kambing yang rentan.
- Tidak ada vaksin capripox rekombinan generasi baru yang tersedia secara komersial.

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Penggunaan antimikroba dalam pengobatan diare pada sapi: tinjauan sistematis

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Tinjauan Sistematis

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Abstrak

Tujuan dari penelitian ini adalah untuk melakukan tinjauan sistematis literatur ilmiah yang mengevaluasi efikasi dan efikasi komparatif antimikroba (AMs) untuk pengobatan diare pada anak sapi. Studi yang memenuhi syarat adalah uji coba terkontrol non dan acak yang mengevaluasi intervensi AM terhadap kontrol positif dan negatif, dengan setidaknya satu dari hasil berikut: skor konsistensi tinja, demam, dehidrasi, nafsu makan, sikap, penambahan berat badan, dan kematian. Empat database elektronik digeledah. Judul dan abstrak (tiga peninjau) dan teks lengkap (dua peninjau) disaring. Sebanyak 2.899 studi diambil; 11 studi memenuhi kriteria inklusi. Risiko bias dinilai. Sebagian besar penelitian memiliki pelaporan desain dan hasil uji coba yang tidak lengkap. Delapan penelitian membandingkan AM dengan kontrol negatif (plasebo atau tanpa pengobatan).n =6) dan kematian (n =6). Studi yang memenuhi syarat mengevaluasi intervensi dan hasil yang sangat berbeda; dengan demikian, meta-analisis tidak dilakukan. Risiko penilaian bias mengungkapkan kekhawatiran dengan pelaporan fitur uji coba utama, termasuk definisi penyakit dan hasil. Bukti yang tidak cukup tersedia dalam literatur ilmiah untuk menilai kemanjuran AM dalam mengobati diare anak sapi.

Perkenalan

Alasan

Gangguan gastrointestinal adalah salah satu penyakit paling umum pada anak sapi perah yang belum disapih: sekitar 21% anak sapi perah di operasi AS terpengaruh dan 76% di antaranya menerima pengobatan antimikroba (AM) (NAHMS-USDA,2018; Urieet al.,2018). Demikian pula, diare adalah alasan utama untuk pengobatan AM di peternakan sapi (Waldneret al.,2013). Tujuan utama terapi AM pada anak sapi yang mengalami diare adalah untuk mencegah bakteremia dan menurunkan jumlah bakteri coliform pada usus halus (Smith,2015). Namun, para ahli merekomendasikan bahwa perawatan AM harus dibatasi pada pedet penggosok yang menunjukkan tanda-tanda klinis penyakit sistemik (Constableet al.,2008).

Di AS, ada sejumlah AM dengan persetujuan Food and Drug Administration (FDA) untuk pengobatan penyakit gastrointestinal pada anak sapi (klortetrasiklin, ampisilin, amoksisilin, oksitetrasiklin, tetrasiklin, dan sulfametazin; FARAD,2020). Sebagian besar obat AM yang disetujui FDA termasuk dalam kelas penisilin atau tetrasiklin, masing-masing dikategorikan sebagai AM yang kritis dan sangat penting untuk pengobatan manusia (WHO,2019). Meskipun AM banyak digunakan untuk profilaksis, metafilaksis, dan pengobatan penyakit infeksi pada pedet (Urieet al.,2018), bukti yang divalidasi tentang kemanjuran AMs untuk pengobatan gangguan pencernaan pada anak sapi masih kurang (Smith,2015).

Penggunaan AM merupakan ancaman bagi kesehatan masyarakat di seluruh dunia, karena merupakan salah satu pendorong utama munculnya resistensi antimikroba (AMR; Van Boeckelet al.,2015; SIAPA,2015; CV FDA,2018). Oleh karena itu, penggunaan obat AM yang penting secara medis pada hewan penghasil makanan telah diusulkan sebagai strategi kunci untuk menjaga keefektifan obat AM yang tersedia saat ini (WHO,2015; CV FDA,2018; OIE,2018). Bukti yang akurat dan tidak memihak tentang kemanjuran terapeutik AM untuk mengobati penyakit menular diperlukan untuk berhasil merancang program penatalayanan AM berbasis bukti (Sargeantet al.,2019a).

Kemanjuran perawatan AM harus dinilai dalam uji coba terkontrol acak multi-lengan (RCT), tetapi ini jarang tersedia dalam literatur ilmiah. Jadi, metode sintesis penelitian RCT dua lengan dapat digunakan untuk mengevaluasi kemanjuran AM (O'Connoret al.,2019). Tinjauan sistematis (SR) dan meta-analisis (MA) adalah alat yang ampuh yang dapat memberikan informasi yang valid secara ilmiah tentang ruang lingkup dan kesimpulan literatur yang ada tentang perawatan AM untuk diare pedet. Metode sintesis ini diperlukan untuk merancang berbasis bukti

pedoman pengambilan keputusan yang dapat dimasukkan dalam program penatalayanan AM untuk ternak.

Tujuan

Tujuan pertama dari penelitian ini adalah untuk melakukan SR untuk menilai literatur ilmiah tentang efikasi dan efikasi komparatif pengobatan AM untuk diare pada pedet di bawah usia 6 bulan. Tujuan kedua adalah melakukan MA untuk mengevaluasi kemanjuran obat AM dibandingkan dengan tidak adanya pengobatan, pengobatan non-AM alternatif, atau obat AM lain yang digunakan untuk mengobati diare pada pedet di bawah usia 6 bulan.

Metode

Protokol dan pendaftaran

Sebuahaprioriprotokol tinjauan dikembangkan sesuai dengan Item Pelaporan Pilihan untuk Tinjauan Sistematis dan Protokol Meta-Analisis (PRISMA-P; Moheret al.,2015) dan diarsipkan di repositori online University of California eScholarship (https://escholarship.org/uc/item/0nw528h4). Selain itu, protokol tersebut dipublikasikan di situs Systematic Review for Animals and Food (SYREAF) (http://www.syreaf.org/ protokol). Amandemen protokol dijelaskan di bawah ini dan mencakup pertanyaan saringan, risiko penilaian bias, dan tindakan ringkasan.

Kriteria kelayakan

Kriteria kelayakan, strategi pencarian, dan pertanyaan penyaringan dirancang berdasarkan format pertanyaan PICOS (Jenis Populasi-Intervensi-Perbandingan-Hasil-Studi; EFSA,2010; O'Connoret al.,2014a). Populasi penelitian adalah anak sapi perah dan sapi potong di bawah usia 6 bulan pada saat pendaftaran studi. Intervensi yang menarik adalah pemberian AM oral atau injeksi (antimikroba; antibiotik dan obat antiprotozoal) setelah mengamati tanda-tanda klinis diare atau setelah memaparkan hewan ke patogen penyebab diare (studi tantangan). Perbandingan yang menarik adalah tidak adanya pengobatan (misalnya plasebo, tanpa pengobatan), pengobatan non-AM alternatif (misalnya ekstrak herbal, probiotik, laktoferin, larutan rehidrasi oral), atau pengobatan AM lainnya (misalnya, AM digunakan sebagai kontrol positif). Hasil yang menarik terbatas pada kematian, kesehatan [misalnya skor konsistensi tinja (FCS), darah dalam tinja, dehidrasi (DH), nafsu makan, sikap, atau demam], dan kinerja [misalnya rata-rata pertambahan harian (ADG) dan efisiensi pakan]. Hanya penelitian yang menilai kemanjuran AM untuk mengobati hewan yang didiagnosis diare berdasarkan tanda klinis yang relevan. Studi yang secara eksklusif berfokus pada pelepasan feses patogen dikeluarkan. SR terbatas pada penelitian primer termasuk non-, quasi-, dan RCT dengan setidaknya satu AM dan satu kelompok pembanding. Hanya publikasi peer-review yang diambil, dan 'literatur abu-abu' (literatur yang tidak diterbitkan secara formal, seperti tesis dan disertasi, prosiding konferensi, artikel perdagangan, laporan penelitian, dan dokumen kebijakan) tidak disertakan (Dickersinet al., 1994). Studi yang memenuhi syarat harus ditulis dalam bahasa Inggris dan tersedia untuk umum, meskipun tidak harus akses terbuka. Periode pencarian didasarkan pada cakupan database, dan tidak ada batasan tanggal publikasi yang diterapkan.

Strategi pencarian dan sumber informasi

Strategi pencarian dirancang oleh pustakawan akademik (EDF) kesehatan dan kedokteran hewan yang berpengalaman, dengan masukan dan daftar kutipan referensi dari pakar konten (CBC dan NSR). Artikel yang relevan diidentifikasi oleh peneliti utama (CBC) dan kata kunci serta istilah pengindeksan ditambang melalui Medline (melalui PubMed, 1966–2020) dan Abstrak CAB (melalui CAB Direct, 1972–2020). Setelah mengembangkan strategi pencarian di CAB Abstracts dan PubMed, pencarian tersebut diterjemahkan oleh EDF ke Scopus (melalui Scopus, 1970–2020) dan Biosis (melalui Web of Science, 1926–2020). Kata kunci dari referensi yang relevan dikumpulkan dan dibandingkan dengan kata kunci yang digunakan dalam pencarian sebelumnya. Penganalisis Yale MeSH (http://mesh.med.yale.edu/) juga digunakan untuk membandingkan Tajuk Subjek Medis umum di seluruh artikel. Pakar konten mengidentifikasi kata kunci atau istilah pengindeksan berdasarkan patogen utama dan AM yang relevan. Selama pemutaran, CBC melakukan pencarian manuskrip yang relevan dan ulasan menggunakan metode bola salju dan pencarian kutipan (https://libguides.library.uu.nl/PiL). Pencarian literatur dilakukan dari 1 hingga 2 Juli 2019, dan pembaruan pencarian dilakukan pada 29 Juni 2020. Semua studi diekspor ke Mendeley (Mendeley Ltd., Elsevier), di mana kutipan duplikat dihapus. Strategi pencarian yang digunakan untuk semua basis data dijelaskan dalam materi Tambahan (SM) 1.

Proses seleksi

Perangkat lunak manajemen Covidence SR (Veritas Health Innovation, Melbourne, Australia) digunakan untuk mengelola penyaringan judul dan abstrak dari semua kutipan yang diambil dalam pencarian. Tiga peninjau dengan latar belakang kedokteran hewan dan ilmu hewan dilatih tentang pertanyaan format PICOS sebelum menyaring judul (CBC, LLS, dan MBA), abstrak (CBC dan LLS), dan teks lengkap (CBC dan LLS). Pertanyaan saringan yang termasuk dalam protokol diuji beta dengan 40 kutipan, dan kemudian dimodifikasi untuk kejelasan jika diperlukan. Untuk pertanyaan saringan judul dan abstrak, kemungkinan jawabannya adalah 'tidak', 'mungkin/tidak jelas', dan 'ya'. Referensi dipindahkan ke tahap berikutnya jika semua judul dan pertanyaan penyaringan abstrak dijawab 'ya' atau 'mungkin/tidak jelas'. Untuk pertanyaan saringan teks lengkap, kemungkinan jawabannya adalah 'tidak' dan 'ya'. Referensi dimasukkan dalam SR jika semua pertanyaan penyaringan teks lengkap dijawab 'ya'. Referensi dikecualikan jika semua pengulas menjawab 'tidak' untuk satu atau lebih pertanyaan. Ketidaksepakatan pada inklusi manuskrip diselesaikan dengan konsensus dan jika perlu, peneliti tambahan (NSR) dikonsultasikan. Pertanyaan saringan terakhir yang digunakan adalah:

Pemutaran judul

(1) Apakah judul menunjukkan sapi sebagai subjek penelitian?
(2) Apakah judul menggambarkan penggunaan pengobatan AM?

Penyaringan abstrak

(1) Apakah abstrak menggambarkan percobaan terkontrol?
(2) Apakah abstrak menggambarkan penelitian tentang diare pada pedet?
(3) Apakah abstrak menggambarkan satu atau lebih kelompok intervensi rejimen pengobatan AM?
(4) Apakah abstrak melaporkan setidaknya satu hasil yang terkait dengan penyembuhan atau kinerja klinis?

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Penyaringan teks lengkap

Pada tahap penyaringan akhir ini, enam pertanyaan sebelumnya dan pertanyaan berikut digunakan:

(1) Apakah usia pendaftaran ternak subjek≤6 bulan?
(2) Apakah AM diberikan setelah diagnosis diare atau timbulnya gejala klinis?
(3) Apakah studi mengevaluasi hasil klinis pengobatan AM?

Studi mengevaluasi kemanjuran penggunaan AM dalam pengendalian (metafilaksis) dan pencegahan (profilaksis) penyakit, sebagaimana didefinisikan oleh American Veterinary Medical Association (AVMA,2020), dikeluarkan. Studi di mana perawatan AM diberikan sebagai promotor pertumbuhan, dan studi dengan data primer yang tidak jelas atau tidak ada pelaporan tidak dipertimbangkan. Alasan pengecualian manuskrip dicatat pada tingkat ini.

Proses pengumpulan data

Proses ekstraksi data selesai mengikuti panduan dari Sargeant dan O'Connor (2014). Dua peninjau (CBC dan LLS) secara independen menggunakan spreadsheet yang telah dirancang sebelumnya untuk mengumpulkan data (Excel 2010, Microsoft Corp., Redmond, WA). Ketidaksepakatan ekstraksi data diselesaikan dengan diskusi sampai konsensus tercapai; jika diperlukan, resensi ketiga (NSR) dikonsultasikan. Data tingkat studi termasuk populasi, intervensi, pembanding, dan hasil untuk setiap studi independen. Data populasi termasuk: ras, jenis kelamin, usia pendaftaran, perumahan, kriteria inklusi, dan ukuran sampel. Intervensi dan data tingkat pembanding diekstraksi dan termasuk: proses pengacakan, ukuran kelompok, fitur pengobatan (bahan aktif, dosis, rute, panjang, dan frekuensi), perawatan komplementer (misalnya terapi cairan dan obat antiinflamasi), dan fitur personel yang memberikan perawatan (misalnya pelatihan atau kebutaan). Selain itu, patogen (mis genus dan spesies) dan jenis infeksi (misalnya studi tantangan atau infeksi alami) diekstraksi. Data hasil yang diekstraksi meliputi: jenis, fitur evaluasi (misalnya metode penilaian, periode evaluasi, dan frekuensi pengukuran), dan fitur personel yang menilai hasil klinis (misalnya pelatihan atau kebutaan). Definisi kegagalan dan keberhasilan pengobatan, jika tersedia, diambil – tanpa modifikasi – dari manuskrip asli. Efek ringkasan dari hasil diekstraksi dari data yang disesuaikan (jika tersedia) atau tidak disesuaikan serta ukuran variabilitas yang sesuai. Selain itu, signifikansi dan variabilitas hasil yang dilaporkan dicatat bila tersedia [misalnya standar deviasi, kesalahan standar, rasio odds, risiko relatif, interval kepercayaan (CI), dan studi tantangan atau infeksi alami) diekstraksi. Data hasil yang diekstraksi meliputi: jenis, fitur evaluasi (misalnya metode penilaian, periode evaluasi, dan frekuensi pengukuran), dan fitur personel yang menilai hasil klinis (misalnya pelatihan atau kebutaan). Definisi kegagalan dan keberhasilan pengobatan, jika tersedia, diambil – tanpa modifikasi – dari manuskrip asli. Efek ringkasan dari hasil diekstraksi dari data yang disesuaikan (jika tersedia) atau tidak disesuaikan serta ukuran variabilitas yang sesuai. Selain itu, signifikansi dan variabilitas hasil yang dilaporkan dicatat bila tersedia [misalnya standar deviasi, kesalahan standar, rasio odds, risiko relatif, interval kepercayaan (CI), dan studi tantangan atau infeksi alami) diekstraksi. Data hasil yang diekstraksi meliputi: jenis, fitur evaluasi (misalnya metode penilaian, periode evaluasi, dan frekuensi pengukuran), dan fitur personel yang menilai hasil klinis (misalnya pelatihan atau kebutaan). Definisi kegagalan dan keberhasilan pengobatan, jika tersedia, diambil – tanpa modifikasi – dari manuskrip asli. Efek ringkasan dari hasil diekstraksi dari data yang disesuaikan (jika tersedia) atau tidak disesuaikan serta ukuran variabilitas yang sesuai. Selain itu, signifikansi dan variabilitas hasil yang dilaporkan dicatat bila tersedia [misalnya standar deviasi, kesalahan standar, rasio odds, risiko relatif, interval kepercayaan (CI), dan fitur evaluasi (misalnya metode penilaian, periode evaluasi, dan frekuensi pengukuran), dan fitur personel yang menilai hasil klinis (misalnya pelatihan atau kebutaan). Definisi kegagalan dan keberhasilan pengobatan, jika tersedia, diambil – tanpa modifikasi – dari manuskrip asli. Efek ringkasan dari hasil diekstraksi dari data yang disesuaikan (jika tersedia) atau tidak disesuaikan serta ukuran variabilitas yang sesuai.

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Risiko penilaian bias

Risiko bias pada tingkat hasil dinilai secara independen oleh tiga peninjau (CBC, RBL, dan LLS) menggunakan Cochrane Risk of Bias Tool for Randomized Trials (Sterneet al.,2019). Lima domain yang umum digunakan (bias yang timbul dari proses pengacakan, bias karena penyimpangan dari intervensi yang dimaksudkan, bias karena data hasil yang hilang, bias dalam pengukuran hasil, dan bias dalam pemilihan hasil yang dilaporkan) dan domain baru (bias terkait dengan definisi penyakit; SM 2) dinilai. Seperti dijelaskan di bawah, pertanyaan pensinyalan dimodifikasi mengikuti pendekatan yang dijelaskan oleh Sargeantet al. (2019a,2019b) dalam studi sintesis ternak sebelumnya. Dalam domain proses pengacakan, pertanyaan 'apakah urutan alokasi acak?' telah dimodifikasi untuk 'apakah penelitian ini diacak?'. Jawaban atas pertanyaan ini dimodifikasi menjadi 'mungkin tidak' jika penelitian tidak melaporkan data tentang pembuatan urutan, 'mungkin ya' jika penelitian melaporkan alokasi urutan acak tetapi bukan proses pengacakan, dan 'ya' jika penelitian melaporkan alokasi acak. komponen dalam proses pembangkitan urutan (mis. pembangkit bilangan acak komputer). Juga, pertanyaan penyembunyian urutan alokasi tidak dimasukkan karena kecil kemungkinannya bahwa seorang pekerja peternakan, produsen, atau peneliti akan memiliki preferensi perlakuan untuk anak sapi yang diberikan. Dalam domain mengenai penyimpangan dari intervensi yang dimaksud, pertanyaan 'apakah peserta mengetahui intervensi yang ditugaskan kepada mereka selama uji coba?' selalu dijawab 'tidak', karena 'peserta' dalam semua penelitian adalah betis. Domain ini juga menanyakan tentang pembutakan personel studi; untuk keperluan SR ini, pengasuh hewan dan/ atau orang yang bertanggung jawab untuk memberikan pengobatan adalah personel penelitian yang relevan. Risiko alat bias diuji dengan tiga studi untuk memastikan konsistensi di seluruh peninjau (Sargeant dan O'Connor, 2014). Peninjau dilatih tentang risiko alat bias, dan ketidaksepakatan antara peninjau diselesaikan dengan konsensus untuk memutuskan keputusan akhir. Hasil yang dipilih untuk penilaian bias adalah keparahan FCS atau diare, tetapi jika tidak dilaporkan, durasi diare digunakan sebagai gantinya.

Sintesis hasil

Seperti yang dijelaskan dalam protokol penelitian, tujuan SR ini adalah melakukan MA untuk mengevaluasi kemanjuran AM dalam pengobatan diare anak sapi. SR kami mengidentifikasi beberapa manuskrip yang memenuhi syarat; ada variabilitas yang luas dalam intervensi dan hasil di seluruh studi. Kelangkaan literatur ilmiah dan heterogenitas di antara studi membuatnya tidak layak untuk menjawab pertanyaan ulasan. Dengan demikian, tidak ada sintesis kuantitatif yang dapat dilakukan, dan heterogenitas tidak dinilai secara formal. Mengikuti pedoman PRISMA, hasil studi dirangkum dalam petak hutan untuk tujuan visualisasi.

Tindakan ringkasan

Ukuran efek [rasio risiko (RR) atau perbedaan rata-rata] dihitung untuk hasil paling umum yang dilaporkan pada tingkat kelompok: tingkat keparahan diare (atau skor tinja) dan kematian pedet. Untuk data kategorikal, perbedaan rata-rata dan 95% CI dihitung menggunakan alat online OpenEpi (https://www.openepi.com/Mean/t_testMean. htm); pooled standard error yang dilaporkan di setiap manuskrip asli digunakan dalam perhitungan ini. Untuk data biner, RR dan 95% CI dihitung menggunakan Perangkat Lunak Statistik MedCalc versi 20.0.5 (Perangkat Lunak MedCalc, Ostend, Belgia). Untuk perhitungan RR, pedet yang mendapat intervensi dianggap terpapar, dan pedet yang diberi pembanding dianggap tidak terpapar. Untuk FCS atau diare, RR dihitung menggunakan kasus diare ringan sampai berat pada pedet yang terpajan dan tidak terpajan. Analisis post-hoc tidak diperlukan ketika manuskrip melaporkan ukuran efek sebagai RR.

Hasil

Karakteristik studi

Hasil di bawah hanya sesuai dengan hasil SR, karena MA tidak dapat dilakukan karena kelangkaan studi dan perbedaan dalam intervensi dan hasil di antara studi yang dipilih. Pencarian mengambil 2899 publikasi dari mana 102 manuskrip teks lengkap dinilai kelayakannya (Gambar 1). Secara total, 11 manuskrip

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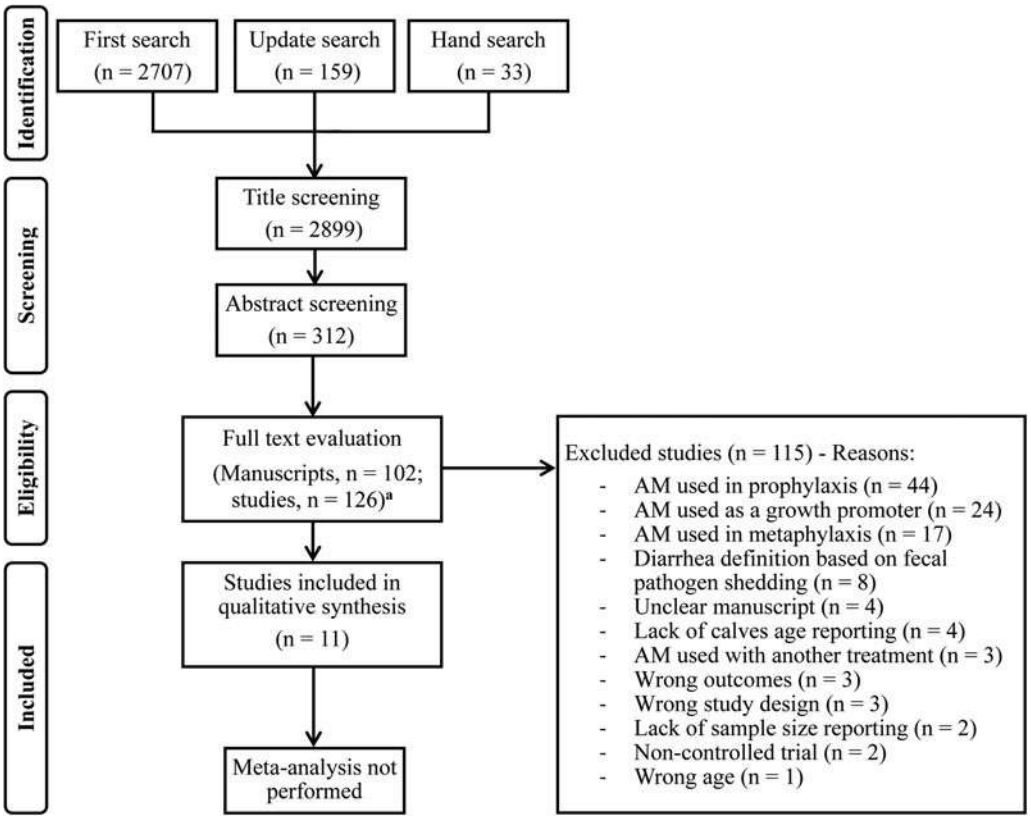

Gambar 1.Diagram alir menggambarkan pemilihan studi yang memenuhi syarat untuk tinjauan sistematis tentang kemanjuran antimikroba dalam pengobatan diare pedet (Diadaptasi dari pedoman PRISMA).A102 manuskrip teks lengkap yang berisi 126 studi independen.

Tabel 1.Karakteristik uji coba yang memenuhi syarat menyelidiki kemanjuran AM dalam pengobatan diare betis

Belajar	Negara	Perumahan (peternakan)	N	UsiaA	Keturunan jenis	Agen etiologi utama
Tantangan						
Melalui air (1977)	Inggris	NR	42	5–10 hari	NR	E.coli
Fecteauet al. (2003)	Amerika Serikat	Universitas/penelitian	29	Saat lahir	Produk susu	Salmonella typhimurium
Lofstedtet al. (1996)	Kanada	Universitas/penelitian	30	≤6 jam	Produk susu	E.coli
Ollivettet al. (2009)	Amerika Serikat	Universitas/penelitian	23	Saat lahir	Produk susu	Cryptosporidium parvum
Schnyderet al. (2009)	Swiss	Universitas/penelitian	6	1–3 hari	NR	C. parvum
Silvaet al. (2010)	Brazil	NR	12	10–15 hari	NR	Salmonella Dublin
Putihet al. (1998)	Inggris	NR	38	1–2 w	NR	E.coli
Infeksi alami						
Keagunganet al. (2002)	Prancis dan Belgia	Komersial	184	≤5 hari	Daging sapi	E.coli
Grimshawet al. (1987)	Inggris, Prancis, dan Jerman	Universitas/penelitian	452	3–10 hari	Produk susu	E.coli
Sheldon (1997)	Britania Raya	Komersial	65	1–30 hari	Produk susu	E.coli
Sunderlandet al. (2003)	Prancis dan Jerman	Komersial	402	7–90 hari	Keduanya	E.coli

NR, tidak dilaporkan.
AUsia saat pendaftaran.

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berisi 11 studi unik memenuhi semua kriteria inklusi dan dimasukkan dalam SR. Karakteristik utama dari 11 studi terpilih dijelaskan dalamTabel 1. Empat studi melaporkan sumber pendanaan [swasta (Lofstedtet al.,1996; Fecteauet al., 2003), publik (Silvaet al.,2010), atau campuran (Olivettet al., 2009)] sedangkan tujuh tidak. Tidak ada penelitian yang memberikan perhitungan ukuran sampel, dan pengacakan tidak jelas dalam satu penelitian (Bywater,1977).

Fitur intervensi dan pembanding

Kelompok intervensi (perlakuan) dan pembanding (kontrol) dijelaskan dalamMeja 2. Tidak ada penelitian yang memberikan informasi tentang pelatihan personel yang memberikan perawatan, dan hanya dua penelitian yang melaporkan personel yang membutakan (Sheldon, 1977; Ollivett et al.,2009). Karena intervensi yang tidak relevan, satu atau lebih kelompok (lengan) tidak dipertimbangkan: (1) pedet yang tidak ditantang dirawat atau tidak dirawat (Fecteauet al.,2003; Schnyderet al.,2009; Silva et al.,2010); (2) AM yang dikombinasikan dengan perawatan lain (Bywater,1977; Silvaet al.,2010); dan (3) AM diberikan sebagai intervensi profilaksis (Schnyderet al.,2009).

Hasil dan definisi

Hasil klinis

Hasil klinis paling umum yang dievaluasi (FCS, suhu, DH, nafsu makan, dan sikap) dijelaskan dalamTabel 3. Variabel klinis lain yang dievaluasi termasuk posisi mata (Lofstedtet al., 1996) dan darah dalam tinja, tenesmus, dan refleks menghisap (Grandemangeet al.,2002). Dalam tiga penelitian, penilai hasil dilaporkan dibutakan dan diidentifikasi sebagai dokter hewan (Sunderlandet al.,2003), siswa dokter hewan (Ollivettet al.,2009), atau peneliti (Putihet al.,1998); tetapi delapan penelitian tidak memberikan informasi ini.

Hasil kinerja

Satu studi menilai ADG (Ollivettet al.,2009). Pertambahan berat badan dievaluasi dalam 6 studi (Bywater,1977; Grimshawet al.,1987; Putihet al.,1998; Fecteauet al.,2003; Schnyderet al.,2009; Silva et al.,2010), namun, satu studi tidak melaporkan hasil (Schnyder et al.,2009). Hanya satu manuskrip yang melaporkan alat atau metode yang digunakan untuk menimbang anak sapi (skala digital; Ollivettet al.,2009).

Definisi kesehatan

Lima studi melaporkan definisi diare (Bywater,1977; Grimshawet al., 1987; Keagunganet al.,2002; Sunderland et al.,2003; Ollivettet al.,2009); itu secara eksklusif didasarkan pada FCS tetapi deskripsi dan sistem poin skornya sangat bervariasi di seluruh studi. Lima studi menggunakan istilah 'diare' tetapi tidak memberikan definisi (Lofstedt et al.,1996; Putihet al.,1998; Fecteau et al.,2003; Schnyderet al.,2009; Silvaet al.,2010), dan satu penelitian mendefinisikan kejadian kesehatan berdasarkan FCS abnormal tanpa menggunakan istilah 'diare' (Sheldon,1997). Dua penelitian melaporkan kegagalan dan keberhasilan pengobatan (Sheldon,1997; Keagungan et al.,2002), tetapi istilah 'kegagalan' tidak didefinisikan di Sheldon (1997).

Hasil dari hasil tertentu

Kematian

Kematian pedet dilaporkan dalam enam penelitian; RR yang dihitung untuk setiap studi direpresentasikan sebagai petak hutan (Gambar 2). RR untuk tiga dari perbandingan (Amoksisilin vs Tanpa pengobatan; Sulbaktam: Ampisilin vs Plasebo; Ampisilin vs. Plasebo) lebih menyukai intervensi relatif terhadap kontrol (CI tidak termasuk 1).

Keparahan diare

Tujuh studi melaporkan tingkat keparahan diare (Lofstedtet al., 1996; Sheldon,1997; Putihet al.,1998; Keagunganet al., 2002; Sunderlandet al.,2003; Ollivettet al.,2009; Silvaet al., 2010). Namun, satu studi (Grandemangeet al.,2002) tidak dipertimbangkan karena pelaporan yang tidak lengkap. Keparahan diare dilaporkan sebagai RR dalam satu manuskrip (Olivettet al.,2009) dan dihitung dalam lima manuskrip [perbedaan rata-rata (n =2); RR (n =3); Gambar 3]. Tidak ada perbandingan yang disukai intervensi relatif terhadap pembanding.

Hasil tambahan

Ringkasan dari semua efek pengobatan yang signifikan secara statistik yang dilaporkan di masing-masing dari 11 studi disediakan di SM 3. Tiga studi melaporkan penilaian efek samping setelah intervensi; dua studi menemukan tidak adanya efek samping (Lofstedtet al., 1996; Sunderlandet al.,2003); dan satu studi mengamati peningkatan keparahan diare setelah pengobatan AM (Schnyderet al.,2009). Satu studi menginformasikan kekambuhan pada tanda-tanda klinis setelah menyelesaikan AM dan intervensi kontrol positif (Grandemangeet al., 2002).

Risiko penilaian bias

Risiko bias pada tingkat hasil didasarkan pada tingkat keparahan diare (atau FCS; Lofstedtet al.,1996; Sheldon,1997; Putihet al., 1998 ; Keagunganet al.,2002; Sunderlandet al.,2003; Ollivettet al.,2009; Silvaet al.,2010) atau durasi diare (Bywater,1977; Grimshawet al., 1987; Fecteauet al.,2003; Schnyderet al.,2009). Hasil penilaian risiko bias untuk setiap domain ditunjukkan pada tingkat studi (Gambar 4) dan sebagai proporsi di semua studi yang disertakan (Gambar 5).

Diskusi

Anak sapi perah dan sapi sering terkena gangguan pencernaan dan diobati dengan AMs (Waldneret al.,2013; NAHMS-USDA,2018); Namun, tidak jelas apakah AMs efektif untuk pengobatan gangguan gastrointestinal betis (Smith,2015). Karya ini bertujuan untuk mendukung pengembangan pedoman penggunaan AM pedet dengan menilai literatur ilmiah tentang kemanjuran dan kemanjuran komparatif dari pengobatan AM yang berbeda untuk diare pada anak sapi di bawah usia 6 bulan. Meskipun diare pada anak sapi paling sering terjadi selama 2 bulan pertama kehidupan (periode Prasapih), kami memilih kriteria usia yang inklusif karena waktu penyapihan dan usia saat kejadian diare dapat berbeda dengan manajemen (misalnya sistem produksi, ras, dan negara). SR kami mengidentifikasi 11 studi yang relevan; namun demikian, jumlah penelitian yang terbatas dan perbedaan dalam intervensi (kelas AM dan jenis agen patogen) menghalangi kami untuk melakukan evaluasi MA (Valentine et al.,2010). Secara keseluruhan, studi yang memenuhi syarat menunjukkan bahwa keparahan diare (n =4, tantangan) dan kematian (n =3, tantangan;n =3, infeksi alami) secara numerik lebih rendah setelah intervensi AM; tetapi hanya tiga dari studi tersebut menunjukkan perbedaan statistik yang signifikan untuk keparahan diare (n =1) dan kematian [tantangan (n =1) dan infeksi alami (n =1)].

SR sebelumnya yang mengevaluasi kemanjuran AM pada ternak juga tidak dapat menyelesaikan MA karena heterogenitas

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Meja 2.Intervensi dan kelompok pembanding dari studi termasuk dalam SR kemanjuran AMs dalam pengobatan diare betis

	Intervensi					Pembanding				
Belajar	Bahan aktif	Dosis[A]	Rute	Panjang[B]	Frekuensi[C]	Bahan aktif	Dosis[A]	Rute	Panjang[B]	Frekuensi[C]
Tantangan										
Melalui air (1977)	Amoksisilin	TD 400 mg	PO	2 hari	q12h	Tidak ada perawatan	–	–	–	–
						Cairan rehidrasi oral	TD 2000 ml	PO	2 hari	q12h
Fecteauet al. (2003)	Ceftiofur	5 mgkg^{-1}	AKU	5 hari	q24j	Tidak ada perawatan	–	–	–	–
Lofstedtet al. (1996)	Sulbaktam: ampisilin	3,3:6,6 mg/kg^{-1}	AKU	3–7 hari	q24j	Plasebo	TD 3 ml	AKU	3–7 hari	q24j
	Ampisilin	6 mgkg^{-1}	AKU	3–7 hari	q24j					
Ollivettet al. (2009)	Nitazoxanide	TD 1504 mg	PO	5 hari	q12h	Plasebo	–	PO	5 hari	q12h
Schnyderet al. (2009)	Nitazoxanide	15 mgkg^{-1}	PO	10 hari	q12h	Tidak ada perawatan	–	–	–	–
Silvaet al. (2010)	Florfenicol	20 mgkg^{-1}	AKU	0–2 hari	q48h	Tidak ada perawatan	–	–	–	–
Putihet al. (1998)	Danofloksasin	1,25 mg/kg^{-1}	AKU	3 hari	q24j	Plasebo	1ml/20kg	AKU	3 hari	q24j
						Baquiloprim: sulfadimidin	10 mgkg^{-1}	AKU	3 hari	q24j
Infeksi alami										
Keagunganet al. (2002)	Marbofloksasin	1 mgkg^{-1}	PO	3–7 hari	q24j	Amoksisilin: asam klavulanat	12,5 mg/kg^{-1}	PO	3 hari	q12h
Grimshawet al. (1987)	Sulbaktam: ampisilin	3,3:6,6 mg/kg^{-1}	AKU	3–7 hari	q24j	Tidak ada perawatan	–	–	–	–
	Ampisilin	6,6 mgkg^{-1}	AKU	3–7 hari	q24j					
Sheldon (1997)	Florfenicol	20 mgkg^{-1}	AKU	0–2 hari	q48h	Baquiloprim: sulfadimidin	20 mgkg^{-1}	AKU	2 hari	q48h
Sunderlandet al. (2003)	Danofloksasin	6 mgkg^{-1}	SC	0–2 hari	q48h	Gentamisin	4 mgkg^{-1}	AKU	3 hari	q12h
						Baquiloprim: sulfadimidin	40 mgkg^{-1}	PO	0–2 hari	q48h

PO, lisan; IM, intramuskular; SC, subkutan; q24h: setiap 24 jam; q12h: setiap 12 jam; q48h: setiap 48 jam.

[A]Dosis dilaporkan sebagai mg kg^{-1}(miligram per kilogram berat badan) atau sebagai mg atau ml TD (dosis total dalam miligram atau mililiter).

[B]Kisaran lama perawatan terkait dengan waktu penyembuhan.

[C]Frekuensi menunjukkan frekuensi yang dilaporkan oleh naskah asli; ini bisa sedikit berbeda dari nilai aslinya.

Tabel 3.Sistem penilaian untuk hasil klinis yang dievaluasi oleh penelitian yang termasuk dalam SR tentang kemanjuran AM dalam pengobatan diare betis

Belajar	Periode evaluasi (hari)A	Konsistensi tinja	Sikap	DH (kriteria)	Nafsu makan	Demam
Tantangan						
Melalui air (1977)	0 sampai 10	0–3B	0–2B	0–2B	NR	NR
Fecteauet al. (2003)	- 4 sampai 13	0–1B	0–4	–	0–3	> 39,2°C
Lofstedtet al. (1996)	0 sampai 7	0–4	0–4	0–3 (kulit)	–	> 40°C
Ollivettet al. (2009)	- 5 sampai 10	1–3C	1–4B	–	–	NR
Schnyderet al. (2009)	- 1 sampai 28	Padat–cairC	–	–	–	–
Silvaet al. (2010)	- 2 sampai 5	0–2B	–	–	–	NR
Putihet al. (1998)	0 sampai 6	0–3B	0–3	Absen–parahB	NR	–
Infeksi alami						
Grimshawet al. (1987)	0 sampai 7	0–3	–	–	–	–
Keagunganet al. (2002)	0 sampai 3, 7	1–5	1–4	1–4 (kulit)	1–2B	> 39,5°C
Sheldon (1997)	0, 2, 4, 10	0–3B	0–4B	NR	–	≥39,5°C
Sunderlandet al. (2003)	0 sampai 11	Absen–parah diare	Absen–parah depresi	Absen–parah (kulit)	–	–

NR, hasil dengan metode penilaian tidak dilaporkan.

ASehubungan dengan onset pengobatan; hari evaluasi menunjukkan periode yang dilaporkan oleh naskah asli, sehingga bisa saja berbeda dari nilai aslinya.

BTidak dijelaskan dengan jelas.

CReferensi disediakan untuk metode sistem penilaian.

intervensi lintas studi primer (O'Connoret al.,2006; Sersanet al.,2019a; 2019b). Meskipun sangat sedikit penelitian yang diidentifikasi dalam SR kami, masuk akal bahwa ada data penelitian tambahan yang valid tetapi belum dipublikasikan dalam publikasi peer-review, terutama jika data dihasilkan untuk mendukung klaim label obat atau jika hasil penelitian menyangkal klaim awal. hipotesis (Polisi,2004; Wellman dan O'Connor,2007). Perlu dicatat bahwa sejumlah besar penelitian dikeluarkan karena mereka mengevaluasi kemanjuran AMs setelah pendekatan pengobatan profilaksis atau metafilaksis, atau karena mereka mendefinisikan 'diare' berdasarkan pelepasan patogen tinja daripada tanda-tanda klinis.

Dalam uji klinis ternak, keakuratan hasil yang diukur telah menimbulkan kekhawatiran karena pelaporan metode dan desain studi yang tidak lengkap (Burns dan O'Connor,2008; Sersanet al., 2009; Jamnyaet al.,2019). Namun, di masa mendatang, standar kualitas uji klinis dapat meningkat, karena beberapa jurnal yang relevan sekarang meminta penulis untuk menggunakan pernyataan REFLECT (O'Connor et al.,2010), panduan untuk desain dan pelaporan standar, sebelum mempertimbangkan manuskrip untuk publikasi. Dalam SR kami, sebagian besar studi dirancang sebagai eksperimen tantangan. Namun, ada keterbatasan yang terkait dengan studi tantangan, karena cenderung menghasilkan efek pengobatan yang berlebihan dan tidak memberikan bukti tingkat tinggi untuk efektivitas intervensi dalam pengaturan komersial (Sargeantet al.,2009,2019a).

Berdasarkan indikasi FDA saat ini, sebagian besar penelitian yang termasuk dalam SR menggunakan AM di luar klaim label. Marbofloxacin (fluoroquinolone spektrum luas untuk anjing dan kucing) dan nitazoxanide (kriptosporidiosis manusia) tidak diberi label di AS untuk digunakan pada sapi atau anak sapi, dan ceftiofur, danofloxacin, dan florfenicol diberi label untuk perawatan betis tetapi untuk penyakit selain diare. Ampisilin dan amoksisilin adalah satu-satunya pengobatan dengan persetujuan FDA untuk pengobatanescherichiacolienteritis pada betis. Namun, panjang pengobatan ampisilin di ini studi berada di luar rekomendasi label. Penggunaan ekstra-label fluoroquinolones (misalnya danofloxacin dan marbofloxacin) dan sefalosporin (misalnya ceftiofur) benar-benar dilarang pada makanan hewan karena tingginya risiko munculnya AMR berdasarkan 'Undang-Undang Klarifikasi Penggunaan Obat Hewan tahun 1994' dan '21 Kode Peraturan Federal 530' (FDA,2021). Juga, rute pemberian berbeda di seluruh studi, secara oral (amoksisilin, marbofloksasin, dan nitazoxanide) atau obat suntik (ampisilin, sulbaktam: ampisilin, ceftiofur, florfenicol, dan danofloxacin). Perbedaan rute pemberian mungkin juga berkontribusi terhadap perbedaan respon pengobatan; pemberian AM secara oral dapat menyebabkan perubahan mikrobioma dan memperparah presentasi diare (Smith,2015).

Selanjutnya, SR kami mengungkapkan bahwa beberapa studi yang relevan termasuk, sebagai intervensi, AM yang paling umum dipilih untuk mengobati diare anak sapi di operasi komersial California (sulfonamid sebagai pilihan pertama; produk ceftiofur sebagai pilihan kedua; Okelloet al.,2021). Meskipun pengetahuan yang diberikan SR tentang kemanjuran dan keefektifan AM itu penting, ini jelas bukan satu-satunya metrik yang penting dalam pemilihan AM. Pekerjaan dokter hewan dan praktisi adalah kunci untuk meningkatkan penggunaan AM pada ternak; faktor relevan lainnya yang memandu dokter hewan dalam pemilihan pengobatan AM adalah algoritme dan protokol pengobatan, pedoman penatalayanan AM, kebijakan peresepan AM lokal, rekomendasi label, hasil pengujian sensitivitas untuk hewan target, dan analisis biaya-manfaat (O'Connoret al.,2019).

Konsisten dengan SR sebelumnya pada ternak, masalah dengan risiko penilaian bias diamati terkait dengan pelaporan yang tidak lengkap dari proses pengacakan dan kebutaan personel yang memberikan perawatan dan penilai hasil (Francozet al., 2017; Sersanet al.,2019b). Pengacakan diklasifikasikan sebagai tingkat risiko tinggi berdasarkan alokasi yang tidak jelas untuk pengobatan karena proses pengacakan tidak dijelaskan, atau pengacakan

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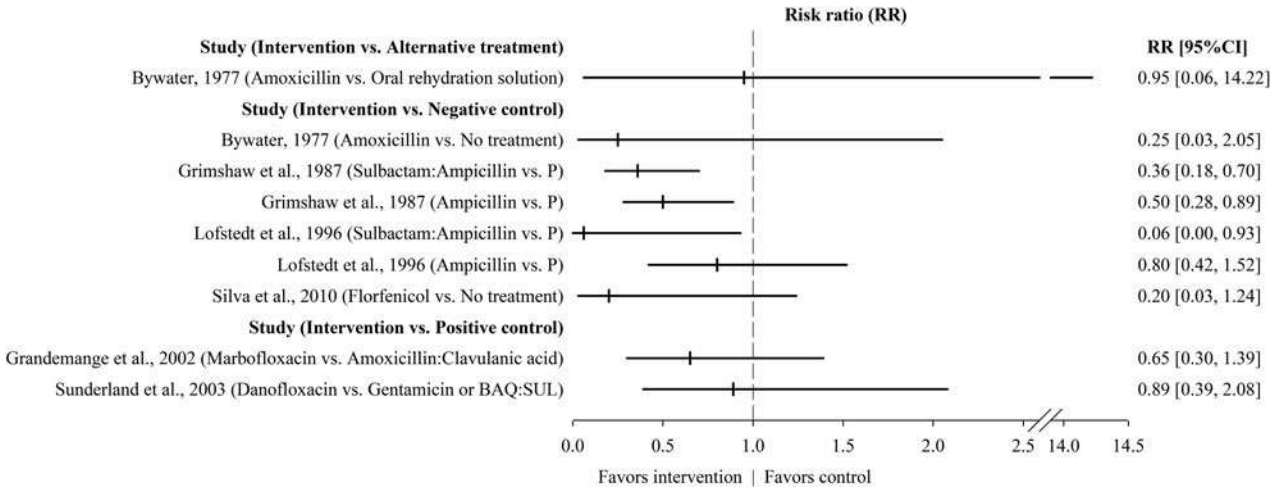
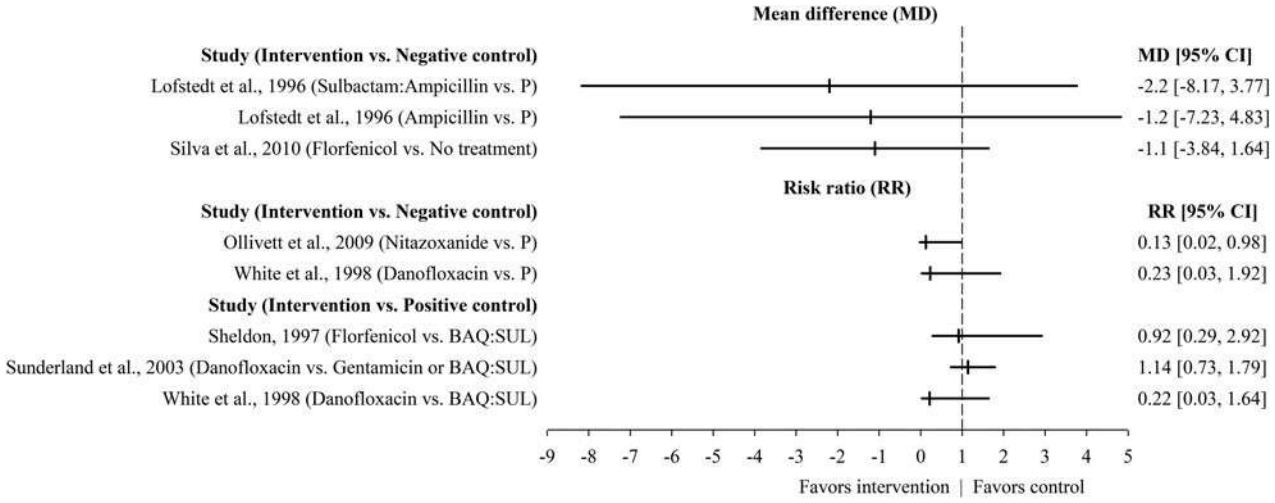


Gambar 2.Forest plot untuk mengilustrasikan hasil tentang mortalitas dari penelitian yang termasuk dalam tinjauan sistematis tentang kemanjuran antimikroba dalam pengobatan diare anak sapi.P =Plasebo;BAQ:SUL =Baquiloprim: Sulfamidin;CI =Interval kepercayaan.

tidak disebutkan. Alasan yang paling sering untuk klasifikasi berisiko tinggi untuk membutakan kedua personel yang memberikan perawatan dan penilai hasil adalah tidak adanya pelaporan yang membutakan. Kurangnya penyamaran personel yang memberikan perawatan dapat memengaruhi perawatan pedet selama penelitian. Demikian pula, penilaian hasil dapat dipengaruhi oleh pengetahuan tentang intervensi yang disampaikan, terutama untuk hasil subyektif, seperti FCS dan DH (Francozet al.,2017; Keraset al.,2019). Semua manuskrip yang relevan kecuali satu terkait dengan perusahaan farmasi, dan itu berpotensi menimbulkan sumber bias. Selain itu, tidak ada penelitian yang termasuk dalam perhitungan ukuran sampel SR kami, yang konsisten dengan ulasan sebelumnya (Haimerlet al.,2012; Jamnyaet al.,2019). Ini mungkin telah memperkenalkan bias publikasi, karena studi yang kurang bertenaga dengan hasil yang tidak signifikan cenderung tidak mencapai jurnal peer-review (Sargeantet al.,2009, 2019a). Alat risiko bias dimodifikasi untuk memperkenalkan domain baru yang terkait dengan definisi penyakit. Sebagian besar penelitian diklasifikasikan dengan bias risiko tinggi berdasarkan domain ini, karena definisi diare hilang di sekitar setengah dari penelitian, dan ketika dilaporkan, definisi tersebut hanya didasarkan pada satu hasil. Hal ini dapat menyebabkan hasil yang bias karena pemberian AM yang tidak perlu pada anak sapi yang diare tanpa tanda-tanda penyakit sistemik (Constableet al.,2008). Hasil kami konsisten dengan SR lain yang menyoroti kurangnya definisi penyakit dalam uji klinis pada sapi (Naqviet al.,2018). Demikian pula, definisi keberhasilan dan kegagalan pengobatan jarang dilaporkan; dengan demikian, sulit untuk secara akurat mengevaluasi hasil studi, metode penilaian kemanjuran pengobatan, dan kemungkinan sumber variasi yang terkait dengan definisi kesehatan (Kelly dan Janzen,1986; Wellman dan O'Connor,2007).

Dalam manuskrip yang relevan, evaluasi tanda-tanda klinis gangguan kesehatan bersifat subyektif dan sangat beragam di seluruh studi. Meskipun FCS dievaluasi dalam semua penelitian, sistem penilaian sangat bervariasi, bahkan ketika FCS memiliki skala numerik yang sama. Selain itu, banyak penelitian memberikan deskripsi yang tidak jelas tentang kategori FCS dengan hanya dua penelitian yang menyebutkan referensi; namun, referensi untuk metode FCS tersebut melaporkan metode evaluasi FCS yang tidak divalidasi, tidak direferensikan, dan tidak lengkap. Tidak ada fitur tinja lain di luar konsistensi yang dievaluasi, dan diare



Gambar 3.Petak hutan untuk mengilustrasikan efek AM pada keparahan FCS atau diare dari studi yang termasuk dalam SR tentang kemanjuran AM untuk mengobati diare pedet. P, plasebo; BAQ:SUL, baquiloprim:sulfadimidin; CI, interval kepercayaan.

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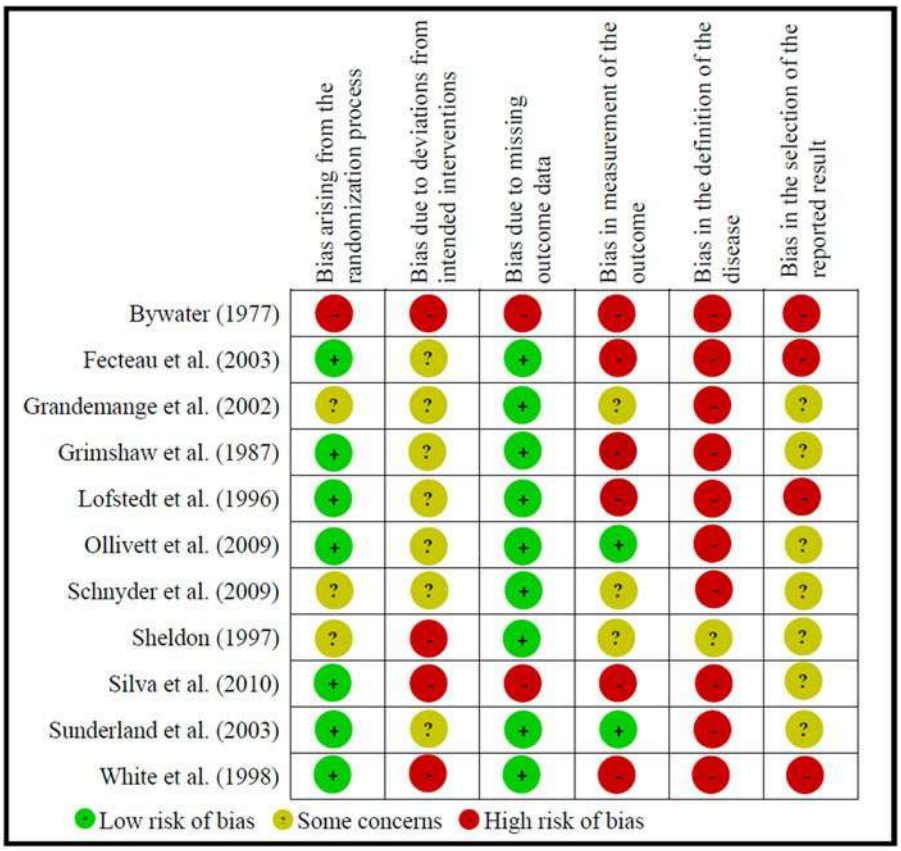

Gambar 4.Ringkasan risiko bias: tinjau penilaian penulis tentang setiap risiko domain bias untuk masing-masing dari 11 studi yang termasuk dalam SR tentang kemanjuran AM dalam pengobatan diare betis.

klasifikasi keparahan diberikan dalam satu studi. Beberapa tanda klinis sekunder yang dievaluasi termasuk DH, demam, anoreksia, dan depresi, tetapi metode evaluasinya bervariasi di seluruh studi, kekurangan referensi, dan subyektif. DH dievaluasi berdasarkan elastisitas kulit tanpa mempertimbangkan lemak tubuh, lokasi kulit, posisi hewan, dan usia (Constableet al.,1998). Empat penelitian mengevaluasi demam, tetapi perbedaan antara ambang batas maksimum dan minimum untuk definisi demam mencapai hampir 1°C di seluruh penelitian, dan tidak ada penelitian yang memperhitungkan kemungkinan ketidakakuratan dalam penilaian suhu tubuh terkait dengan metode fisiologis, lingkungan, dan prosedur (Hill et al.,2016). Demikian pula, sistem penilaian untuk sikap dan nafsu makan didasarkan pada pengukuran empiris dan subyektif, dan sangat berbeda antar studi. Secara keseluruhan, kurangnya metode evaluasi standar di 11 studi yang relevan memprihatinkan, karena keandalan yang rendah baik dalam pengukuran hasil dan definisi kesehatan dapat berkontribusi pada penurunan kekuatan statistik dan dengan demikian estimasi efek pengobatan yang terlalu rendah atau terlalu tinggi (Sargeantet al., 2009). Lebih dari empat dekade yang lalu, pedoman evaluasi kesehatan anak sapi diusulkan untuk membuat pelaporan lebih seragam di seluruh studi penelitian (Larsonet al.,1977); namun, pedoman ini belum diadopsi, kemungkinan besar karena tingkat kerumitannya (Kertz dan Chester-Jones, 2004). Pedoman industri saat ini untuk diare pedet menyarankan untuk membatasi pengobatan AM pada pedet dengan feses encer yang juga menunjukkan tanda-tanda penyakit sistemik (misal: kurang nafsu makan, DH, lesu, pireksia), darah atau robekan mukosa pada fesesnya, atau infeksi bersamaan (Constableet al.,2008; McGurik, 2008). Tak satu pun dari studi yang relevan mencapai definisi ini; studi tantangan memperlakukan semua hewan yang terpapar, dan dalam studi infeksi alami, pengobatan hanya didasarkan pada FCS. Studi di masa depan harus mengatasi kurangnya standar, kesehatan anak sapi yang tervalidasi definisi, yang menghasilkan keputusan pengobatan heterogen dan definisi penyembuhan. Penggabungan dan kombinasi metode penilaian kesehatan yang tervalidasi adalah kunci untuk secara akurat mengidentifikasi pedet yang sakit, meningkatkan keberhasilan pengobatan, dan meningkatkan kesejahteraan hewan baik di dalam maupun di luar penelitian (McGuirk, 2008; Crameret al.,2016). Selanjutnya, metode penilaian standar akan menyebabkan keseragaman yang lebih besar dalam desain penelitian (Larson et al.,1977), membuat interpretasi dan perbandingan percobaan ternak lebih mudah. Selain itu, hasil objektif, seperti ADG, mortalitas, dan hasil laboratorium, dapat meningkatkan reliabilitas studi dan kemampuan untuk meringkas ukuran efek intervensi. Namun, dalam SR kami, hanya satu penelitian yang menilai ADG, enam penelitian melaporkan mortalitas, dan hasil laboratorium yang dilaporkan sangat beragam dan terbatas pada evaluasi tunggal.

Terakhir, SR ini memiliki beberapa kekuatan; itu mengikuti protokol yang dilaporkan sesuai dengan PRISMA-P (Moheret al., 2015); itu mematuhi pedoman untuk SR di bidang peternakan dan kedokteran hewan (O'Connoret al.,2014a,2014b; Sersan dan O'Connor,2014); strategi pencarian, yang menggunakan banyak basis data elektronik, dirancang dengan dukungan dari pustakawan untuk mengidentifikasi jumlah tertinggi dari studi yang tersedia; dan untuk meningkatkan keandalan proses, penyaringan, ekstraksi data, dan penilaian risiko bias dilakukan secara independen oleh dua atau lebih peninjau dengan latar belakang kedokteran hewan dan ilmu hewan serta dalam metode sintesis penelitian (Sargeant dan O'Connor ,2014).

Di sisi lain, SR kami mungkin memiliki beberapa keterbatasan. Kami tidak menganggap literatur abu-abu sebagai sumber yang relevan. Rata- rata, hanya 50% dari abstrak yang melaporkan hasil RCT mencapai publikasi penuh, dan rasio abstrak-ke-publikasi yang dihitung untuk beberapa konferensi bovine adalah <10% (Dickersinet al.,1994; Penjepitet al.,

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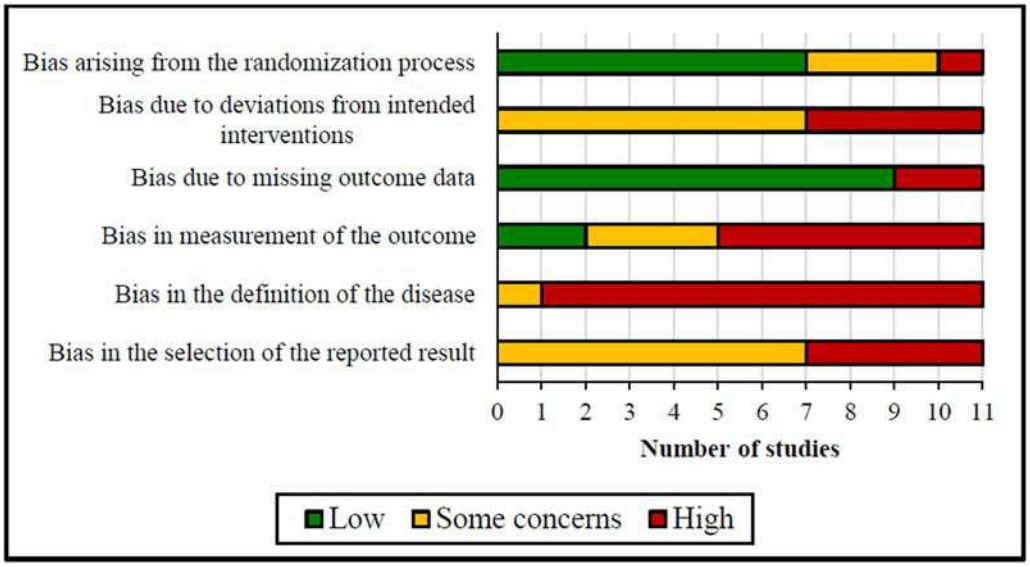

Gambar 5.Grafik risiko bias: tinjau penilaian penulis tentang setiap risiko domain bias yang disajikan sebagai persentase di semua studi yang disertakan (n =11) di SR khasiat AMs dalam pengobatan diare betis.

2010). Dengan demikian, mengecualikan studi ini dapat menghasilkan presisi yang lebih rendah dalam estimasi efek intervensi dan dapat mengakibatkan hasil yang bias dengan memperkenalkan bias publikasi (Dickersinet al.,1994; Sersan dan O'Connor,2014). Namun, mengecualikan literatur abu-abu mungkin memiliki dampak terbatas, karena biasanya melibatkan abstrak pendek dengan data yang tidak cukup untuk melakukan metode sintesis penelitian (Burns dan O'Connor,2008; Penjepitet al.,2010; Sersan dan O'Connor,2014). Sumber bias lainnya mungkin adalah pengecualian artikel yang berpotensi relevan yang diterbitkan dalam bahasa selain bahasa Inggris. Dalam kedokteran hewan, dampak pembatasan bahasa masih belum diketahui (Burns dan O'Connor, 2008), sedangkan dalam kedokteran manusia, membatasi bahasa publikasi laporan percobaan ke bahasa Inggris dalam SR intervensi konvensional (misalnya AM) tidak mengubah estimasi efektivitas intervensi (Moheret al., 2003; Phamet al., 2005). Oleh karena itu, dampak pengecualian manuskrip dalam bahasa selain bahasa Inggris kemungkinan kecil dalam SR saat ini.

Kesimpulan

Saat ini, kemanjuran AM dalam pengobatan diare pedet tidak dapat dievaluasi menggunakan metode MA, karena SR mengidentifikasi beberapa penelitian relevan yang menguji intervensi heterogen. SR kami mengungkapkan keterbatasan penting dalam desain dan pelaporan penelitian, yang harus diatasi oleh penelitian di masa depan untuk melakukan evaluasi MA yang berharga tentang kemanjuran AM dalam pengobatan diare betis. Intervensi yang diuji harus mencerminkan pendekatan pengobatan on-farm yang umum, komunitas penelitian perlu mencapai kesepakatan tentang definisi dan sistem evaluasi hasil penyakit diare, dan penelitian harus mematuhi pedoman pelaporan.

Materi tambahan.Bahan tambahan untuk artikel ini dapat ditemukan dihttps://escholarship.org/uc/item/0nw528h4#supplemental.

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Konflik kepentingan.Tidak ada penulis yang memiliki konflik untuk dideklarasikan.

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Assessing the Quality of Bovine Embryos Derived from Metabolically Stressed Oocyte during Maturation using TUNEL

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MAMMS, SAA and KAA designed the study, analysed and interpreted the data and drafted the MS. MAMMS *in vitro* embryo production and TUNEL staining.

Key words
Bovine embryo quality, Metabolic stress, NEFA, Oocyte maturation, Apoptosis, TUNEL

ABSTRACT

The current research aimed to assess apoptotic cell ratio (ACR) via TUNEL staining in bovine embryos produced in vitro from oocytes matured in stressful conditions of elevated concentrations of non-esterified fatty acids (NEFAs). The maturation conditions in the current study were resemble the situation in the oocyte microenvironment of metabolically stressed lactating dairy cows during the post-partum period where the negative energy balance occurred. Oocytes were in vitro matured under elevated levels of NEFAs for 24 h in serum-free maturation media. Obtained zygotes were cultured in synthetic oviduct fluid with 5% FCS for eight days. Blastocyst stages from each treatment group were assessed and evaluated for their quality by determining the ACR by means of TUNEL staining. The presence of palmitic or stearic acid at high concentrations during oocyte maturation increased ACR, whereas oleic acid had no significant effects. The results of the present study concluded that compromised oocyte microenvironment by metabolic stressor such as high NEFAs concentrations which is the situation during the negative energy balance that are happened post-partum in dairy cows could decrease the quality of preimplantation embryos as indicated by the incidence of apoptosis.

INTRODUCTION

Metabolic stressors during the post-partum period in high yielding dairy cows are generated from the negative energy balance and it consequences that are occurred during this period. These metabolic stressors are vast and include a lot of biochemical and metabolic adaptation in blood and follicular fluid (FF). These metabolic stressors may include elevated concentrations of non-esterified fatty acids (NEFA) in growing oocyte microenvironment (i.e. follicular fluid) (Shehab-El-Deen *et al*., 2010). In an in vitro model when NEFAs, such as palmitic and stearic acids, added to oocyte maturation medium with similar concentrations associated with negative energy balance resulted embryo quality have been declined (Shehab-El-Deen *et al*., 2009). In the tropical and subtropical regions, high ambient temperature during summer is the main reason for postpartum dairy cattle subfertility (Ealy *et al*., 1993; Shehab-El-Deen *et al*., 2010). Summer heat stress worsen the situation of negative energy balance and its associated elevated NEFAs (Shehab-El-Deen *et al*., 2010). At early stage of lactation, high lactating cows are more susceptible to high ambient temperatures, because their accelerated metabolic heat production (Blackshaw and Blackshaw, 1994). Accordingly, if the growing oocyte is being subjected to stress conditions during its development processes, its quality will be negatively affected and subsequently embryonic development (Butler, 2003). Some of these stress conditions include biochemical changes in oocyte microenvironment associated with negative energy balance postpartum (Leroy *et al*., 2004; Shehab-El-Deen *et al*., 2010). The stress conditions that present in oocyte microenvironment have late effects on pregnancy, parturition and post-natal development (Greve and Callesen, 2005). The biochemical adaptations during the beginning of lactation in high lactating dairy cows can become morbid and therefore may interfere with cow fertility (Butler and Smith, 1989; Leroy *et al*., 2004; Shehab-El-Deen *et al*., 2010; Rodney *et al*., 2018). Altered

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levels of non-esterified fatty acids (NEFAs) in FF have already linked with changes in oocyte quality (Leroy *et al.* 2004; Shehab-El-Deen *et al*., 2010). High concentrations of NEFAs during the negative energy balance period (NEB) in high lactating dairy cows have already linked with extensively studied reduced fertility (Robinson 1999; Rukkwamsuk *et al*., 1999; Vanholder *et al*., 2005; Shehab-El-Deen *et al*., 2010). This assumption has been proved by addition of NEFAs, such as oleic acid (OA), palmitic acid (PA) and stearic acid (SA) at concentrations, which prevail in FF during NEB to oocyte maturation conditions of embryo production protocol *in vitro* in bovine. Inclusion of saturated fatty acids to bovine oocyte maturation medium had obvious deleterious effects on oocyte quality and developmental competence, whereas the monounsaturated OA had no effect (Leroy *et al*., 2005; Shehab-El-Deen *et al*., 2010). Assessing the competence of bovine embryos obtained from oocyte subjected to stress conditions has become crucial in embryo transfer program that are used to bypass the negative effects of heat stress in dairy cows and research purposes (Vandaele *et al*., 2007). The terminal deoxynucleotidyl transferase mediated dUTP nick end labeling (TUNEL) technique is used to assess bovine preimplantation embryo quality by detecting apoptosis as apoptotic cell ratio (ACR) and hence DNA fragmentation (Spanos *et al*., 2000; Paula-Lopes and Hansen, 2002).

The current study aimed to assess the quality of bovine preimplantation embryos obtained from oocyte exposed to high NEFAs concentrations during in vitro maturation by means of TUNEL staining to determine the incidence of apoptosis and hence embryo quality.

MATERIALS AND METHODS

In vitro *production of embryos*

Bovine embryos were produced in vitro as described earlier (Shehab-El-Deen *et al*., 2009). Briefly, the ovaries of slaughtered bovine were collected and processed within 2 h from slaughtering. The ovaries, after removing of mesovaria, were rinsed many times in warm physiological saline containing kanamycin (25mg/m). only follicles of diamtere ranged between 4 and 8 were aspirated

In vitro *maturation*

Good oocyte based on appearance and cumulus cells layers were cultured in serum free maturation conditions in groups 60 oocyte per well in 500 µL modified bicarbonate buffered TCM199 with Earle's and glutamine and supplemented with murine epidermal growth factor (EGF) (20 ng/mL) for 22 h at 38.5°C in 5% CO_2 in air.

In vitro *fertilization*

Oocytes were washed and transferred to in vitro fertilization medium 500 µL IVF-TALP (60 oocytes/well) consisting of bicarbonate buffered Tyrode solution, with BSA (6 mg/mL) and heparin (25 µg/mL). Frozen-thawed bovine semen from the same bull was separated over a Percoll-density gradient (45 and 90%, Pharmacia, Uppsala, Sweden) and washed. Sperm concentration was adjusted in IVF-TALP. Bovine spermatozoa were added to the well containing oocyte in IVF-TALP at a final concentration of 10^6 spermatozoa/mL. Inseminated oocytes were incubated for 20-24 h at 38.5°C in 5% CO_2 in air.

In vitro *culture*

The probable zygotes were subjected to vortex to get rid of cumulus cells and spermatozoa. Fertilized oocytes were washed several times and moved on to SOFaa supplemented with 5% FCS and were cultured in 50 µL droplets of SOFaa in groups of 25 zygotes per well under mineral oil for 8 days under low oxygen conditions; 5% O_2, 5% CO_2 and 90% N_2.

Addition of non-esterified fatty acids (NEFAs) to maturation medium

The studied non-esterified fatty acids; oleic acid (OA), palmitic acid (PA) or stearic acid (SA) were dissolved in absolute ethanol. The three fatty acids were tested in 3 replicates (1800 oocytes), in addition to negative and positive control groups. Control media consisted of normal maturation medium without NEFAs or ehtanol (negative control) or with absolute ethanol (positive control) (Leroy *et al*., 2005).

Detection of apoptosis

Bovine *in vitro* produced blastocysts at day eight after insemination from each treatment group were subjected to TUNEL staining (In Situ Cell Detection kit, Boehringer, Mannheim, Germany) for detection of apoptosis according to Gjørret *et al*. (2003). Breifly, blastocysts yielded in each group were washed in phosphate buffer saline (PBS) twice for 2 min at 37°C and then were fixed in 4% paraformaldehyde and kept until staining. Blastocysts were permeabilized in Triton X-100 (0.5% in PBS) for 1 h at room temperature in the dark. TUNEL positive and TUNEL negative blasotcysts were incubated for 1 h in the dark at 37°C in DNase (50 Units/mL in PBS). Durig DNase step, the blastocysts from other groups were kept in polyvinyl pyrrolidone (PVP) in PBS at room temperature. For TUNEL solutions, blastocysts from all treatment groups and TUNEL positive control were incubated in fluorescein dUTP and terminal deoxynucleotidyl transferase in the dark for one h (37°C). Meantime, the

TUNEL-negative control blastocysts were not subjected to transferase and was incubated in nucleotide mixture only. Thereafter, all blastocysts were incubated in RNase (50µg/ml in PBS) for 1 h in the dark at room temperature. Subsequently, all blasotcysts were subjected to 0.5 % propidium iodide (PI) for nuclei stainimg during one h at room temperature. Finally, blastocysts were washed quickly in PVP in PBS and mounted in 1, 4-diazabicyclo (2.2.2) octane (DABCO) droplet on slides with vaseline bridges. Blastomeres that are TUNEL Positive were read by fluorescence microscopy. Propidium iodide helped to indentify normal, condensed or fragmented nuclei and count the total cell number, while TUNEL-positive nuclei appeared yellowish-green, condensed or fragmented.

Apoptotic cell ratio was assessed as percentage of TUNEL-positive blastomeres either in inner cell mass or in trophectoderm.

Statistical analyses

The percentages of apoptotic cells in blastocyst from different treatment groups were analyzed using mixed model analyses of variance with group as fixed factor and replicate as random factor. The same model was used to evaluate the percentage of blastocyst at 8 dpi. For all analyses, differences were considered to be statistically significant at the 5% level. Statistical analyses were performed in SPSS version 14.00

RESULTS

No significant differences could be detected in the blastocyst yield or expanded blastocyst yield at 8 dpi (Table I). However, the addition of the three fatty acids to maturation medium significantly decreased total cell number and trophectoderm cell number of the resulting embryos (P<0.01) (Fig. 1). The same results were found in inner cell mass for oleic and palmitic acids but not for stearic acid comparing to negative control group. When apoptosis in expanded blastocysts was assessed (Fig. 2), it was found that stearic and palmitic acids during maturation increased ACR in inner cell mass in the resulting embryos (P<0.01). However, in trophectoderm, palmitic acid only increased the incidence of apoptosis (P<0.01). The same effect of palmitic acid was found in total cell number (P<0.01). Whereas the addition of ethanol during *in vitro* maturation did not affect ACR in resulting embryos in the current study.

DISCUSSION

Current study tests the effects of oocyte maturation conditions on subsequent embryo quality. It is well known that oocyte of low quality led to slow developing embryos and high incidence of apoptosis during preimplantation embryonic development (Vandaele *et al*., 2007). Non-esterified fatty acids have been widely reported to induce apoptosis in granulosa and cumulus cells of developing ovarian follicles. Furthermore, NEFA present in oocyte micro-environment or in maturation medium could negatively affect oocyte quality and developmental competence. Moreover, high levels of NEFA are determine for follicular cells as they adversely affect steroidogenesis and proliferation processes (Leroy *et al*., 2004; 2005; Vanholder *et al*., 2005; Shehab-El-Deen *et al*., 2010; Baddela *et al*., 2020). Additionally, NEFAs may also contribute to the problem of the polycystic ovaries as they might upregulate Sertoli cell marker-9, an androgenic transcription factor and downregulating its estrogenic counterpart in grnaulosa cells (Yenuganti and Vanselow, 2017). Accordingly, assessing the quality of bovine embryos resulted from oocytes subjected to high NEFAs levels during maturation becomes an important approach for determining fertility outcomes in high yielding dairy cows during negative energy balance- or heat stress-associated metabolic stress. The occurrence of apoptosis in in vitro produced bovine embryos can be detected at the time of embryonic genome activation (i.e. around the eight-cell stage) using TUNEL (Byrne *et al*., 1999; Matwee *et al*., 2000; Gjørret *et al*., 2003). It is well demonstrated that increased non-esterified fatty acids concentrations in oocyte micro-environment hinder oocyte quality and have consequences on presumptive embryos quality, as well. At morula and blastocyst stages, certain blasotmeres undergo apoptosis as a physiological mechanism to eliminate weak or

Table I. Blastocyst and expanded blastocyst yield (mean±SE) at day 8 post insemination of bovine oocyte matured in the presence of palmitic acid (C16:0), stearic acid (C18:0) or oleic acid (C18:1). Negative control was maturation medium without fatty acids or ethanol and positive control group was maturation medium with the addition of absolute ethanol.

Treatment group	No. cultured oocytes	% blastocyst	% Expanded blastocyst
Palmitic acid	318	28.15±4.34	17.02±2.58
Stearic acid	318	27.2±3.89	16.02±2.3
Oleic acid	333	32.73±3.9	18.15±2.4
Negative control	314	30.46±2.75	15.76±1.63
Positive control	300	29.89±2.62	16.46±1.55

Blastocyst and expanded blastocyst percentages were calculated from cultured oocytes.

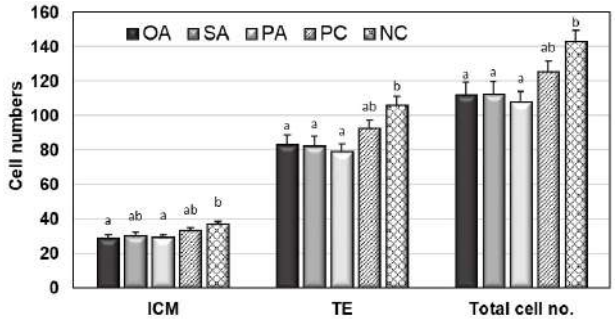

Fig. 1. Cell number (mean±SE) of inner cell mass (ICM), trophectoderm (TE) and total cell number in bovine embryos (8 dpi) derived from oocytes matured either in oleic acid (OA) (C18:1), stearic acid (SA) (C18:0) or palmitic acid (PA) (C16:0). Negative control (NC) was maturation medium and positive control group (PC) was maturation medium with the addition of pure ethanol. [a, b] Bars bearing different superscripts differ within each category; inner cell mass (ICM), trophectoderm (TE) or total blastocyst cell number *(P<0.01)*.

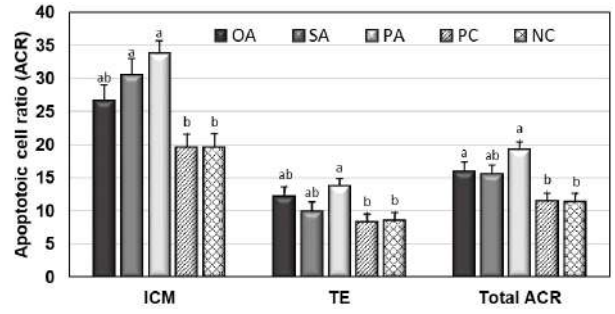

Fig. 2. Apoptotic cell ratio (ACR) (mean±SE) in inner cell mass (ICM) and trophectoderm (TE) of bovine embryos (8 dpi) derived from oocytes matured either in palmitic acid (PA) (C16:0), stearic acid (SA) (C18:0) or oleic acid (OA) (C18:1). Negative control (NC) was maturation medium and positive control group (PC) was maturation medium with the addition of pure ethanol. [a, b] Bars bearing different superscripts differ within each category; inner cell mass (ICM), trophectoderm (TE) or total blastocyst cell number *(P<0.01)*.

damaged cell to balance cell propagation and death, furthermore, programed cell death plays a critical role to sweep the balstomeres with altered genome from further development, which is crucial in *in vitro* produced blastocyst subjected to stressful conditions (Ramos-Ibeas *et al*., 2020). Accordingly, the incidence of apoptosis in embryos resulted from oocyte subjected to stressful condition seems to be an adaptive mechanism to ensure that unhealthy cells and early embryos do not progress in development, avoiding long-term detrimental effects.

Actually, both PA and SA caused a significant increase in ACR in inner cell mass compared to control groups either positive (ethanol) control group or negative control group. However, there was no significant difference among the three studied fatty acids in ACR either in ICM or in trophobalst. Increased ACR in ICM, may be due to qualitative and⁄ or quantitative changes in the cytoplasmic lipids or the cell membrane. When intracellular lipids were removed from porcine embryos, they became more tolerance to cryogenic injury, which is indicating that these lipids may hinder embryo quality and development (Nagashima *et al*., 1995). Moreover, Abe *et al*. (2002) proved that lipid accumulated in embryos could impair their quality and cryotolerance (Abe *et al*., 2002).

Fatty acids in oocyte micro-environment are able to accumulate inside the oocytes and potentially altering oocyte lipid content and composition (Kim *et al*., 2001; Adamiak *et al*., 2005; Leroy *et al*., 2008). Kim *et al*. (2001) stated that PA, OA and SA are the three predominant fatty acids in bovine oocytes. Furthermore, in vitro maturation of bovine oocyte in the presence of serum altered triglyceride and total cholesterol contents, which is evident that lipids and fatty acids may be incorporated into the oocyte cytoplasm (Kim *et al*., 2001). Their findings suggest that both maturation conditions, oocyte morphology and cryopreservation, can affect fatty acid composition in bovine oocytes. Shehab-El-Deen *et al*. (2009) confirmed that exposure of bovine oocyte during maturation to stressful concentrations of NEFAs had a carry-over effects on embryo quality. However, it is still not known whether apoptosis is involved of the observed inferior embryo quality. More specifically, Palmitic acid may be an important negative element in this regard (Van Soom *et al*., 2001). It is well demonstrated that Fatty acids in culture medium can be up taken by the embryo to be used for the renewal of its membrane lipids (Pratt, 1980); accordingly, any changes in cell membrane during oocyte maturation could affect developing embryos. However, Matwee *et al*. (2000) concluded that as embryonic development proceed the bovine embryos develop resistance to apoptosis. Moreover, it has been previously shown that SA and PA induce apoptosis in the cumulus cells, which definitely affect oocyte maturation through gap junction and probably also embryo development may be affected in a negative way. Possible pathway by which fatty acids induce apoptosis is through affecting signal transduction, because they are implicated in several signal transduction pathways. Both stearic acid and linoleic acid have been implicated in stimulation of protein kinase C leading to apoptosis (Yu *et al*., 2001; Eitel *et al*., 2003). The results of the current study concluded that in vitro maturation of bovine oocytes in stressful levels of PA and SA can have

carry-over effects on embryo quality, leading to increased apoptosis in inner cell mass. However, PA only increased apoptosis in trophectoderm. However, more studies are still needed to elucidate the mechanism through which NEFA induced apoptosis.

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Statement of conflict of interest

The authors have declared no conflict of interest.

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Research Article

The Spread of Lumpy Skin Disease Virus across Southeast Asia: Insights from Surveillance

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Lumpy skin disease (LSD) is a notifiable, transboundary disease, causing substantial economic and welfare impacts in cattle. Prior to October 2020, LSD had not been reported in Southeast Asia; however, on 5 October 2020, Vietnam reported the first case in the region. This study aimed to investigate the initial spread of LSD virus (LSDV) in cattle across Southeast Asia between October 2020 and October 2021. LSD outbreak data were accessed from the World Organisation for Animal Health (WOAH) World Animal Health Information System (WAHIS) database and analysed to investigate this spread via epidemic curves, disease maps, clustering, and descriptive statistics. During the epidemic period, 866 LSD outbreaks were reported from six Southeast Asian countries, consisting of 1,758,923 susceptible cattle, 93,465 cases, 5,936 deaths, and 1,117 cattle culled. Analysis revealed a propagated epidemic throughout Southeast Asia, with four major peaks in case numbers across Thailand and Vietnam. Three clusters of reported outbreaks were identified, and Thailand was found to be the epicentre of the outbreak in the region, which could reflect reporting bias and underreporting from other countries in Southeast Asia. High morbidity and mortality rates were reported, particularly in Thailand, Vietnam, and Cambodia, likely reflective of infection in a naïve population and lack of an effective vaccination program. These findings are in contrast to what has generally been described in other parts of the world. Furthermore, studies should examine the risk factors associated with high morbidity and mortality rates in this region. A greater understanding of LSD epidemiology in Southeast Asia will assist farmers and governments to implement effective control and prevention strategies that reduce the spread of disease to other regions and the potentially devastating impacts of LSD.

1. Introduction

Lumpy skin disease (LSD) is a notifiable, transboundary disease, causing substantial economic and welfare impacts in livestock. LSD is caused by the lumpy skin disease virus (LSDV), belonging to the family *Poxviridae* and genus *Capripoxvirus* [1]. LSD primarily affects cattle, water buffalo, and wild ruminants; however, few reports of infections in wildlife have been noted [2]. All ages and breeds are susceptible to the disease, but infection is most commonly reported—and is most severe—in young cattle, underweight cattle, and those in peak lactation or immunocompromised [3]. Whilst disease mortality is usually low (1–3%), morbidity rates are high, averaging 5–45% [2, 4]. The condition is characterised by circumscribed skin nodules 2–6 cm in diameter, generally located on the neck, legs, tail, and back [5]. Clinically affected animals also commonly present with pyrexia, enlarged lymph nodes, depression, reduced milk yield, and abortion [2]. LSDV can remain viable in the environment for up to 35 days, with the main sources of LSDV being necrotic skin lesions, scabs, and blood [6]. Transmission can occur via blood-sucking arthropods, such as mosquitoes and *Stomoxys* spp., contaminated feed and water, and bodily secretions [7]. Increased outbreaks and case numbers occur in summer and during wet periods when vector species are abundant, suggesting viral spread is linked primarily to vector transmission [7, 8].

Endemic initially in Africa, LSD has spread in parts of Europe via the movement of infected animals and vector transmission, amplified by seasonally linked outbreaks [7, 9].

LSDV environmental persistence and various modes of transmission create challenges for control and prevention programs worldwide. Despite this, the widespread use of live-attenuated vaccines during the Balkans outbreak (2015–2017) proved successful in controlling this epidemic [10]. In addition, early outbreak detection, stamping out (culling affected and cattle suspected of being infected), and cattle movement restrictions have assisted in control programs worldwide [10]. Although these control measures have been implemented in endemic areas, LSDV has recently spread to Asia, with reports from China, India, Bangladesh, and Nepal [11, 12]. Subsequently, the first reported outbreak of LSD in Southeast Asia occurred in Vietnam (Huu Lung District, Lang Son Province) in October 2020 [13]. During 2020-2021, the disease spread to five other Southeast Asian countries: Cambodia, Laos, Malaysia, Myanmar, and Thailand. Due to the recent nature of LSD occurrence in Southeast Asia, current knowledge regarding its status and outbreak trends within the region is sparse. Given the extent of this outbreak and lack of knowledge surrounding LSD in Southeast Asia, it is critical to investigate LSD epidemiological patterns in this region. Together with welfare concerns, data from previous outbreaks indicate LSD to be a substantial financial burden to producers because of reduced milk yield, trade restrictions, and treatment and prevention costs [2, 14]. Therefore, investigating trends in LSD epidemiology in Southeast Asia could assist in reducing further spread and mitigate the consequential impacts of the disease.

The aim of this study was to investigate and map the spread of lumpy skin disease in cattle across Southeast Asia between October 2020 and October 2021, during its early spread phase. An analysis of outbreaks was undertaken to determine patterns in case numbers, locations, timing of outbreaks, and epidemic progression throughout the region. This investigation was based on data obtained from the World Organisation for Animal Health (WOAH) World Animal Health Information System (WAHIS) database.

2. Materials and Methods

2.1. Data Collection and Management. The locations and dates of reported LSD outbreaks throughout Southeast Asia were sourced from the WOAH. Immediate notifications and follow-up reports were downloaded from the Animal Disease Events collection publicly available at the WAHIS interface (https://wahis.woah.org/#/home; last accessed on 15/04/2022). This interface was accessed each month from the end of the study period (October 2021) until April 2022. The reports that were present in the database at that time were considered to be the final study dataset. LSD outbreaks reported in the WAHIS interface were selected if they occurred in a Southeast Asian country (Brunei, Myanmar, Cambodia, Timor-Leste, Indonesia, Laos, Malaysia, the Philippines, Singapore, Thailand, and Vietnam) between 1 October 2020 and 1 October 2021. Reported cases of LSD were diagnosed by authorities in each country based on clinical signs and nucleic acid detection (PCR assays), as well as necropsies (in Myanmar and Thailand). No additional details on diagnostic procedures were documented in the data that was available. From each WAHIS report, the following information was extracted: report date, outbreak start and end dates (if applicable), outbreak location (latitude/longitude and by name), unit type (village or farm), and number of susceptible animals, cases, deaths, and culled. Reports were filtered to include only cattle; reports of LSD in other *Bovidae* (Buffalo, *Capricornis sumatraensis, Bos frontalis*, and *Bos javanicus*) were excluded due to the small number of reports (37) and low case numbers (115). The data collected were imported into Excel 16.0 (Microsoft, Redman WA), and reports were combined into datasets (by country of origin) for further analysis. Error checking was performed: for each data entry, logical values were checked, and manual checking against the original reports from the WAHIS database was also undertaken.

2.2. Data Analysis. Epidemic day was calculated by assigning day 1 to the first reported case in the region (5 October, 2020), and then each report date was allocated a number relative to this baseline date.

The daily number of cases and outbreak reports for each country were calculated and plotted for the outbreak period, on a normal and a log scale, to produce epidemic curves (Microsoft Excel 16.0). The locations (latitude and longitude) of reported outbreaks were mapped; this was achieved using a shape file of Southeast Asia (DIVA-GIS, geographic coordinate system (GCS) WGS 1984) within a geographic information system (ArcGIS v10.7. ESRI, Redlands, CA). Data points for each reported outbreak were created by using the reported latitude and longitude values. Based on the day each outbreak was reported to occur, a colour ramp (epidemic day green to red [days 1–361]) was used to visualise the epidemic spread of LSD throughout Southeast Asia. The mean centres and one standard deviation directional ellipses (unweighted and weighted by epidemic day and number of cases) were calculated. These visualisation tools were overlayed on the point map of reported outbreaks to describe the progression of the LSD epidemic in Southeast Asia. The weighting of mean centres and directional ellipses used either the epidemic day at each location or the number of cases reported at each location. Thus, locations at which LSD was reported later or more cases were reported influenced the estimated mean centres and directional ellipses more. In this way, whether outbreak time or intensity influenced the distribution of the epidemic could be investigated. In addition to case locations by epidemic day, a map was created based on reported case numbers using a colour ramp (case numbers green to red [0–11520] to visualise the spatial distribution of the number of reported cases in each outbreak.

A retrospective space-time analysis was conducted (SaTScan v9.6, https://www.satscan.org/) to identify clusters present within the WAHIS reported data. The discrete Poisson (population at-risk) model was utilised, which assumes the number of reported cases at each location is Poisson-distributed, i.e., the expected number of cases at each location is proportional to the population size [15].

Therefore, in this analysis, the numerator was the reported number of cases at each location, and the denominator was the number of susceptible cattle at the same location in the same report submitted to WAHIS. These data were scanned for clusters of locations with high attack rates. The maximum spatial cluster size was arbitrarily set to 20% of the population at-risk and the maximum temporal cluster size to 50% of the study period to identify clusters of interest. Identified clusters were interpreted based on the ratio of expected to observed cases, and the statistical significance was evaluated by log likelihood ratios using a Monte-Carlo simulation with 999 iterations. The statistically significant clusters that were identified were mapped (ArcGIS v10.7. ESRI, Redlands, CA) based on the cluster centre (longitude, latitude) and radius (km).

Descriptive analysis was undertaken using Excel 16.0. Morbidity (number of cases ÷ susceptible animals), mortality (number of deaths ÷ susceptible animals), and the culled rate (number of culled ÷ susceptible animals) estimates were calculated as proportions for each report submitted to WAHIS. "Culled" was interpreted as cattle that were culled by authorities or farmers and disposed of due to infection. Analyses for each country also included the number of outbreaks, susceptible numbers, cases, deaths, and culled, as well as the mean, median, and interquartile range (IQR) of the number of cases and epidemic days.

3. Results

Between October 1, 2020, and October 1, 2021, 866 LSD outbreaks were reported from Southeast Asian countries to the WAHIS database (Tables 1 and 2). These reports detailed a total of 1,758,923 susceptible cattle, 93,465 cases, 5,936 deaths, and 1,117 cattle culled (Tables 1 and 3). Outbreaks were first reported from Vietnam (5 October 2020) and Myanmar (9 November 2020), and subsequently from Thailand (29 March 2021), and then finally from Malaysia (10 May 2021), Laos (22 May 2021), and Cambodia (26 May 2021).

Since the number of cases per report was not constant, both cases and reports were plotted to better understand the epidemic. The reported outbreaks across Southeast Asia illustrate a propagated epidemic, with four major peaks in case numbers (Figures 1 and 2). The first peak occurred on day 74 in Vietnam, and the other three peaks occurred on days 220, 238, and 246 in Thailand (Figure 1). The epidemic curves showed Thailand to have experienced an LSD epidemic with concentrated periods of outbreaks and cases, whilst the other countries (Cambodia and Malaysia) experienced more prolonged outbreaks with fewer cases that occurred over a longer period of time (Figures 1 and 2). The majority of the outbreaks ($n = 533$), susceptible cattle ($n = 1{,}738{,}566$), cases ($n = 78{,}968$), and deaths ($n = 5{,}874$) occurred in Thailand, the epicentre of the Southeast Asia outbreak (Tables 1–3; Figure 3). Secondary to Thailand, Vietnam experienced the next highest case numbers ($n = 12{,}703$), followed by Cambodia ($n = 824$). Country-specific epidemic curves are shown in Supplementary figures A and B. As expected, all mean centres calculated (unweighted, case, and epidemic day weighted) were situated in Thailand, with the cases centre northeast and the unweighted and epidemic day centres situated close together and to the south in Thailand (Figure 3). The direction of spread during the study period was north to south with a 3.8° rotation. When weighted by epidemic day (1–361), the direction of spread was very similar (2.3° rotation) to the unweighted analysis, but when weighted by number of outbreak cases reported (0–11520), there was a noticeable northeast shift (41.1° rotation), demonstrating the greater impact of LSD in areas of eastern Thailand during the earlier months of this epidemic (Figure 3).

The median outbreak day followed a similar pattern as to LSD spread throughout Southeast Asia (Table 2). Myanmar only reported one outbreak during the Southeast Asia epidemic, and Laos reported nine outbreaks. The epidemics in Laos and Myanmar had few cases, and shortly after, they officially marked their country's outbreak as resolved, with no further cases since the initial occurrence was reported. The majority of cases in Vietnam occurred on one day of the epidemic (74), followed by a substantial period of time without reports of disease. Subsequently, on day 293 of the epidemic period, cases re-emerged, with a slight increase in reported case numbers towards the end of the study period. Malaysia and Cambodia reported LSD outbreaks later in the epidemic, with case numbers continuing to rise towards the end of the study period. Outbreaks in Thailand began on day 156 of the epidemic, and whilst outbreaks continued to be reported throughout the epidemic period, the majority of cases occurred within 100 days of Thailand's first reported case.

Three major clusters were identified by spatial data analysis and considered to be statistically significant. The primary cluster was centred in east Thailand but included Laos and occurred between 13 May and 30 June 2021. Within this cluster (radius 125 km), there was an observed-to-expected ratio of cases of 9.57 ($P < 0.001$) (Figure 4). The secondary cluster occurred in central Thailand and occurred over a longer time period, between 21 April 21 and 5 July 2021. The radius of this cluster was greater (195 km), with an observed-to-expected ratio of 4.91 ($P < 0.001$) (Figure 4). The tertiary and smallest cluster occurred in northeast Thailand between 17 April and 13 May 2021. Within this cluster (radius 67 km), there was an observed-to-expected ratio of cases of 11.06 ($P < 0.001$) (Figure 4).

Overall, across all six countries, case morbidity was 20.9%, case mortality was 2.7%, and the culled rate was 0.7% (Table 1). Morbidity was highest in Thailand (37.1%) and Cambodia (22.4%), followed by Malaysia (19.5%), Laos (19.1%), Vietnam (18.1%), and Myanmar (9.5%) (Table 1). Mortality was highest in Vietnam (7.7%) and Thailand (7.3%), whilst the other countries had a mortality rate of less than 1.1% (Table 1). The culled rate was highest in Vietnam (4.4%), followed by Thailand (0.03%), with the other countries reporting no cattle culled (Table 1).

4. Discussion

This study provides an overview of the epidemiology of LSDV throughout Southeast Asia in 2020-2021, via

Table 1: Summary statistics of lumpy skin disease (LSD) cases, morbidity, and mortality rates in Thailand, Malaysia, Cambodia, Vietnam, Laos, and Myanmar, reported to the World Organisation for Animal Health (WOAH) World Animal Health Information System (WAHIS) from 1 October 2020 to 1 October 2021.

Parameters	Thailand	Malaysia	Cambodia	Vietnam	Laos	Myanmar	Average	Total
Number of reports	553	267	21	15*	9	1	144.33	866
Number of susceptible cattle	1738566	11271	3907	3098	2018	63	293153.83	1758923
Number of cases	78968	595	824	12703	369	6	15577.5	93465
Number of deaths	5874	1	13	48	0	0	989.33	5936
Number culled	20	0	0	1097	0	0	186.17	1117
Mean morbidity (%)	37.1	19.5	22.4	18.1	19.1	9.52	20.95	—
Minimum morbidity (%)	0.001	0.20	13.33	3.76	14.91	9.52	6.95	—
Maximum morbidity (%)	100	100	41.67	48	20	9.52	53.20	—
Mean mortality (%)	7.3	0.07	1.1	7.7	0	0	2.68	—
Minimum mortality (%)	0	0	0	0	0	0	0	—
Maximum mortality (%)	100	20	6.67	53.57	0	0	30.04	—
Mean culled (%)	0.03	0	0	4.4	0	0	0.73	—
Minimum culled (%)	0	0	0	0	0	0	0	—
Maximum culled (%)	14.08	0	0	15.09	0	0	4.86	—

The total number of reports ($n = 866$), number of susceptible cattle ($n = 1758923$), number of cases ($n = 93465$), number of deaths ($n = 5936$), and number of culled ($n = 1117$) were reported for each country. The morbidity and mortality were calculated as number of cases ÷ number of susceptible cattle and number of deaths ÷ number of susceptible cattle, respectively. The proportion culled was calculated as number culled ÷ number of susceptible cattle. An average was calculated and reported across all countries ($n = 6$). The data was extracted from the WOAH WAHIS (https://wahis.woah.org/#/home). *Vietnam only officially reported 15 outbreaks; however, 2 outbreaks contain suboutbreaks that account for the majority of the cases (outbreak 84273 had 205 suboutbreaks, accounting for 11,520 of the cases and outbreak 84272 has 45 suboutbreaks, accounting for 722 cases).

Table 2: Summary statistics of lumpy skin disease (LSD) reports ($n = 866$) from Thailand, Malaysia, Cambodia, Vietnam, Laos, and Myanmar to the World Organisation for Animal Health (WOAH) World Animal Health Information System (WAHIS) from 1 October 2020 to 1 October 2021.

Parameters	Thailand	Malaysia	Cambodia	Vietnam	Laos	Myanmar	Average
Number of reports	553	267	21	15	9	1	144.33
Minimum epidemic day	1	1	1	1	1	1	1
1st quartile	221	253	300	12	230	35	175.17
Mean	234.4	286.5	321	103.5	235.3	35	205.62
Median	227	275	332	22	230	35	186.83
3rd quartile	249	325	355	183.5	234	35	230.25
Maximum epidemic day	205	145	127	358	31	1	144.5
IQR	28	72	55	171.5	4	0	55.08

Day 1 is assigned to the start date for each group's epidemic. An average was calculated and reported across all countries ($n = 6$). The data was extracted from the WOAH WAHIS (https://wahis.woah.org/#/home).

Table 3: Summary statistics of lumpy skin disease (LSD) cases in Thailand, Malaysia, Cambodia, Vietnam, Laos, and Myanmar, reported to the World Organisation for Animal Health (WOAH) World Animal Health Information System (WAHIS) from 1 October 2020 to 1 October 2021.

Parameters	Thailand	Malaysia	Cambodia	Vietnam	Laos	Myanmar	Average
Number of susceptible cattle	1738566	11271	3907	3098	2018	63	293153.83
Number of cases	78968	595	824	12703	369	6	15577.5
Minimum cases in single report	0	1	6	1	19	6	5.5
1st quartile	3	1	15	7.5	28	6	10.08
Mean	147.60	2.23	39.24	846.87	41	6	180.49
Median	13	1	25	27	42	6	19
3rd quartile	74	2	70	58.5	51	6	43.58
Maximum cases in single report	10317	17	103	11520	78	6	3673.5
IQR	71	1	55	51	23	0	33.5

The number of susceptible animals ($n = 1758923$) and number of cases ($n = 93465$) were reported for each country. An average was calculated and reported across all countries ($n = 6$). The data was extracted from the WOAH WAHIS (https://wahis.woah.org/#/home).

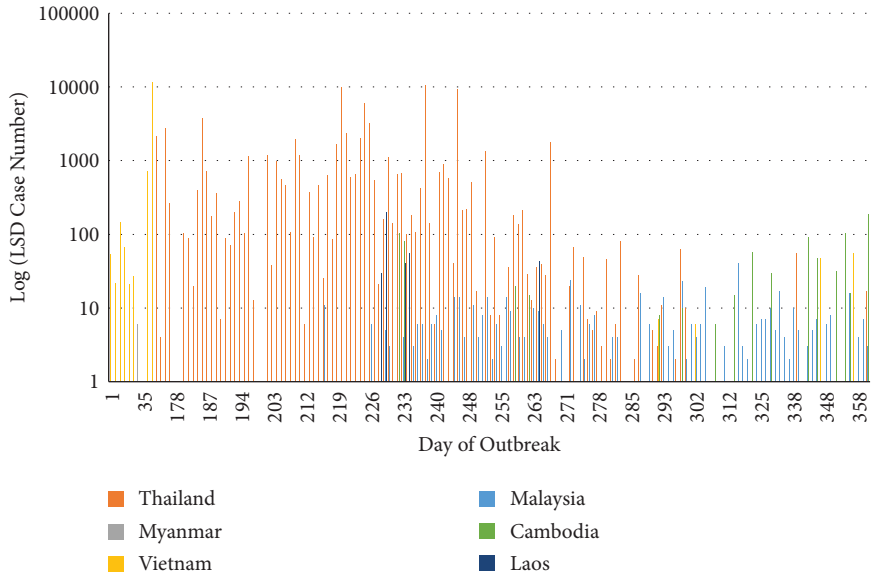

FIGURE 1: Number of lumpy skin disease (LSD) cases (log scale) reported from Thailand, Malaysia, Cambodia, Vietnam, Laos and Myanmar to the World Organisation for Animal Health (WOAH) World Animal Health Information System (WAHIS; https://wahis.woah.org/#/home) from 1 October 2020 to 1 October 2021.

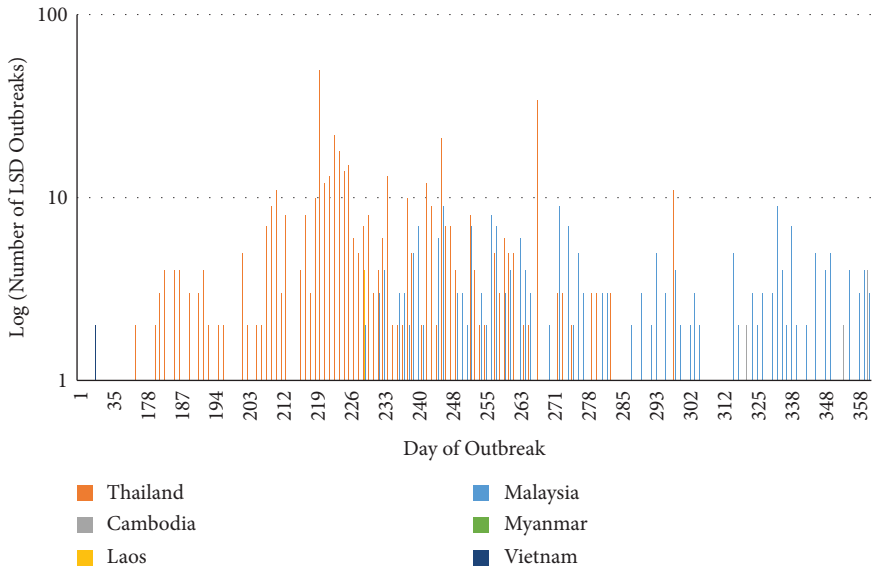

FIGURE 2: Number of lumpy skin disease (LSD) reports (log scale) from Thailand, Malaysia, Cambodia, Vietnam, Laos, and Myanmar to the World Organisation for Animal Health (WOAH) World Animal Health Information System (WAHIS; https://wahis.woah.org/#/home) from 1 October 2020 to 1 October 2021.

descriptive statistics, epidemic curves, disease mapping, and cluster analysis. Compared to what is reported in the literature, we estimated high morbidity and mortality rates in Southeast Asia and identified Thailand as the epicentre of this regional epidemic.

The data analysed in this investigation were limited to what was accessible and reported from each country to the WOAH WAHIS database, presenting a key limitation to this study. As this investigation relied solely on each country reporting information about their LSD outbreaks, there is potential for reporting bias. Countries with frequent reporting likely provided a more accurate description of their epidemic, whereas countries with infrequent reporting, a lack of resources, poor surveillance of LSD cases, and differing policies contribute to the lack of data accuracy. Whilst reporting should be standardised and therefore equivalent across countries, there is no guarantee that this will occur. However, the analysis of reported cases provided some important insights into the spread of LSDV in Southeast Asia during the initial incursion phase. Considering the very large number of cases reported to the WOAH WAHIS database and that LSD

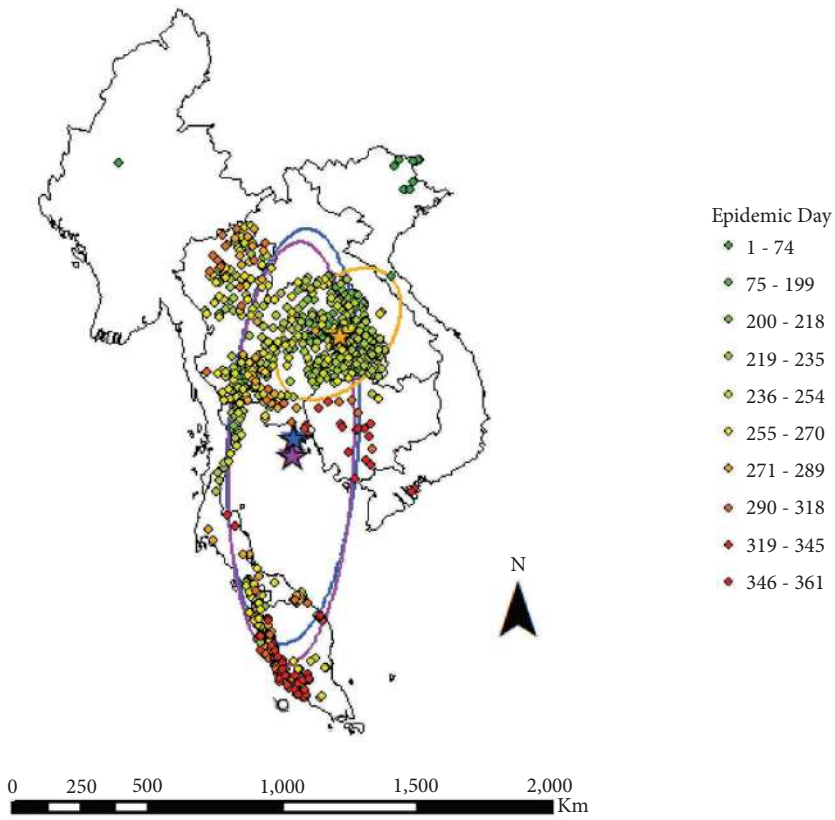

Figure 3: Distribution of lumpy skin disease outbreak sites in Southeast Asia between 1 October 2020 and 1 October 2021. Sites are shaded green to red by epidemic day (1–361). Day 1 = 5 October 2020; day 361 = 1 October 2021. Directional ellipses (1 SD) are overlayed; unweighted (blue) and weighted by cases (orange) and epidemic day (purple). The mean centres indicated by stars; unweighted (blue) and weighted by cases (orange) and epidemic day (purple). Data was extracted from the World Organisation for Animal Health (https://wahis.woah.org/#/home).

was a novel disease syndrome during 2020-2021, the biases inherent in such surveillance data were unlikely to substantially affect the overall conclusions made. Different outbreaks can also be grouped together and reported as single outbreaks. This cluster of reporting creates barriers when inferring farm dynamics and epidemiology trends from data, and cluster detection identified areas where there were reports with higher attack rates than expected (Poisson model), rather than areas with a higher incidence. Unidentified cases throughout Southeast Asia were also likely, with a risk of under-detection due to subtle clinical signs, subclinical cases, or unobservant farmers. Estimates of morbidity and mortality might depend on when outbreaks were investigated and the timeliness of reporting and follow-up reports. We made the assumption that outbreak investigation protocols during this early period of the LSD epidemic in Southeast Asia were broadly consistent, so that systematic bias was minimised. It must be noted that data from outbreaks in Southeast Asia were collated until 15 April 2022 and therefore might differ from any current revisions to the data in the WOAH WAHIS database. Data were updated throughout the study with revisions made periodically to the dataset.

Most cases of LSD were reported from Thailand and Vietnam. Whilst more disease could have been experienced in these countries, it is likely that more effective surveillance systems resulted in more outbreaks being reported. During this early phase of the LSD epidemic in Southeast Asia, methods of control were likely similar across the region, a region in which livestock management systems are typically based on smallholders. Implementation of disease control and prevention, such as the use of vaccines, once a disease becomes endemic will result in changes to the spatiotemporal distribution of disease occurrence. Although more LSD outbreaks were reported from Vietnam and Thailand, the overall consistent spread of LSD through Southeast Asia in 2020-2021 suggests that reporting of the disease varied by country. More uniform surveillance would enable a more detailed epidemiological analysis of this epidemic.

Overall, we estimated a mean case morbidity rate in Southeast Asia, based on reports, of 20.9%, with a very large range from 0.001 to 100%. Across the world, LSD morbidity rates can vary depending on a range of both within and between country factors, with an average rate between 5 and 45% reported [4]. Studies investigating previous epidemics in Asia report similar morbidity rates ranging from 0.3 to

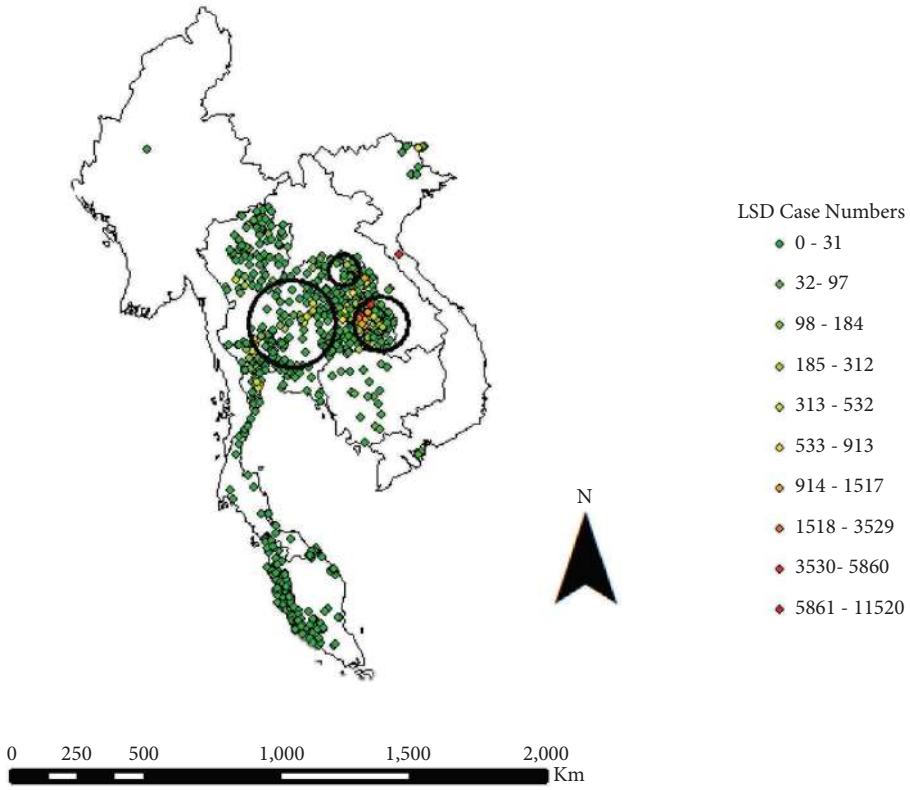

Figure 4: Lumpy skin disease case numbers in Southeast Asia from 1 October 2020 to 1 October 2021. Outbreaks are shaded green to red by case number (0–11520). Primary (13 May to 30 June 2021; east), secondary (21 April to 5 July 2021; west) and tertiary (17 April to 13 May 2021; central) spatiotemporal clusters are overlayed, with observed to expected case numbers being 9.57, 4.91, and 11.06, respectively. The data was extracted from the World Organisation for Animal Health (https://wahis.woah.org/#/home).

30% [12, 16–18]. In contrast, morbidity rates reported from other areas of the world have been lower than in the current study, such as 8.6% in Iraq [19] and 8.7% in Greece [20]. In this study, the highest morbidity rates were estimated for Thailand and Cambodia, 37.1% and 22.4%, respectively. Without further information detailing the management systems in place for affected premises in this study, it is difficult to establish the definite cause for the high morbidity rates. Literature suggests morbidity rates can be influenced by multifactorial issues regarding host susceptibility, the environment, and the pathogen. Cattle breed, host immunological status, vector population, climate, husbandry, management conditions, and LSDV strain are key aspects to consider [2]. With regard to management conditions, studies have found smallholder operations with smaller herds and fewer cattle to have a statistically significant greater morbidity risk, compared to more intensive operations [5]. With smallholder management systems dominating in southeast Asia, this might explain the higher morbidity rates estimated.

The mean mortality rate across Southeast Asia estimated in this study was 2.7%. This estimate is higher than average mortality rates reported in other countries yet remains less than the upper end of the expected range (<10%) [4]. Across other Asian countries, such as India, Hong Kong, Bangladesh, and China, mortality rates of 0 to 0.9% have been reported [12, 16–18]. In other regions in the world, the mortality rate is often low, generally reported to be <3% [19, 20]. The mortality rates investigated in this study showed Vietnam to have the highest (7.7%), closely followed by Thailand (7.3%). These high rates could be due to many reasons, potentially including sampling bias. These two countries had the highest reporting rates for susceptible animals and cases, making their reported outbreak scale much larger than other countries. Other possible reasons for elevated mortality rates include the agro-ecological zones and husbandry management systems affected [21], the entirely naïve cattle populations [22], and lack of access to vaccines. A phylogenetic analysis has indicated LSDV isolates in Thailand to be 99.83% similar to the strains from mainland China, Hong Kong territory, and Vietnam in a potential virulent vaccine-recombinant strain [23]. According to reports submitted to the WOAH WAHIS database, Thailand coordinated a multifaceted control and prevention response to its LSD epidemics. This included movement restrictions on animals in affected provinces, decreased bovine importation, public awareness campaigns to support early detection, distribution of insecticides, and establishing containment zones within a 50 km radius of outbreaks [24]. Early approval of LSD vaccinations by the Thai Food and Drug Administration, followed by a vaccine plan, allowed the first vaccines to arrive in Thailand on 29 May 2021, two months after the first case report in the country [24]. Although the vaccination program was

promptly initiated, LSDV spread had already occurred prior to implementation. It is unclear how the vaccination schedule was executed or if all regions of Thailand had available access, adequate resources, and education to vaccinate their cattle appropriately. The role of vaccination in Southeast Asia requires investigation.

5. Conclusions

This investigation found LSD in Southeast Asia to have generally high morbidity and mortality rates in the epidemics that occurred between 1 October 2020 and 1 October 2021. The lack of an effective vaccine program and the naivety of the Southeast Asian cattle population likely contributed to these high estimates; however, further research on specific risk factors influencing morbidity and mortality rates in Southeast Asia is warranted. Whilst outbreaks were reported from six Southeast Asian countries, Thailand was identified as the epicentre of this regional epidemic during the study period. Vector abundance, strain virulence and transmissibility, management, control, and prevention factors likely contributed to the predominance in this region. To assist in mitigating further spread of disease, particularly to the Asia-Pacific and Oceania regions, future studies should focus on risk factors for LSDV transmission, high morbidity and mortality rates as well as the efficacy of control and prevention strategies in Southeast Asia.

Data Availability

The data are available via the World Animal Health Information System, https://wahis.woah.org/#/home.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

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Supplementary Materials

Supplementary figure A: number of lumpy skin disease (LSD) cases (log scale) reported from each of Thailand, Malaysia, Cambodia, Vietnam, Laos, and Myanmar to the World Organisation for Animal Health (WOAH) World Animal Health Information System (WAHIS; https://wahis.woah.org/#/home), 1 October 2020 to 1 October 2021. Supplementary figure B: number of lumpy skin disease (LSD) outbreaks (log scale) reported from each of Thailand, Malaysia, Cambodia, Vietnam, Laos, and Myanmar to the World Organisation for Animal Health (WOAH) World Animal Health Information System (WAHIS; https://wahis.woah.org/#/home), from 1 October 2020 to 1 October 2021. (*Supplementary Materials*)

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viruses

MDPI

Article

Lumpy Skin Disease Outbreaks in Africa, Europe, and Asia (2005–2022): Multiple Change Point Analysis and Time Series Forecast

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Abstract: LSD is an important transboundary disease affecting the cattle industry worldwide. The objectives of this study were to determine trends and significant change points, and to forecast the number of LSD outbreak reports in Africa, Europe, and Asia. LSD outbreak report data (January 2005 to January 2022) from the World Organization for Animal Health were analyzed. We determined statistically significant change points in the data using binary segmentation, and forecast the number of LSD reports using auto-regressive moving average (ARIMA) and neural network auto-regressive (NNAR) models. Four significant change points were identified for each continent. The year between the third and fourth change points (2016–2019) in the African data was the period with the highest mean of number of LSD reports. All change points of LSD outbreaks in Europe corresponded with massive outbreaks during 2015–2017. Asia had the highest number of LSD reports in 2019 after the third detected change point in 2018. For the next three years (2022–2024), both ARIMA and NNAR forecast a rise in the number of LSD reports in Africa and a steady number in Europe. However, ARIMA predicts a stable number of outbreaks in Asia, whereas NNAR predicts an increase in 2023–2024. This study provides information that contributes to a better understanding of the epidemiology of LSD.

Keywords: lumpy skin disease; change point analysis; time series; outbreaks; forecast; Africa; Europe; Asia

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1. Introduction

Lumpy skin disease (LSD) is an emerging transboundary viral disease that is caused by the lumpy skin disease virus (LSDV), which belongs to the *Capripoxvirus* genus of the *poxviridae* family [1]. Cattle and water buffalo are the primary hosts of this disease [2], but some wild animals, such as giraffes, springboks, and oryxes, can also be infected [3]. Arthropod vectors, such as ticks, biting flies, and mosquitoes, are the mechanical carriers of the LSDV [4–7]. The clinical signs in diseased animals are fever, lacrimation, skin nodules, nasal discharge, skin edema, and enlarged lymph nodes [8,9]. It can also cause reduced milk production and can lead to death. LSD tends to have morbidity up to 90% and mortality of less than 10% [10]. The World Organization for Animal Health (WOAH) has placed LSD on the list of notifiable diseases [11].

In 1929, the first outbreak of LSD occurred in Zambia, and in the next decade, the virus extended to sub-Saharan Africa [12]. LSD was reported outside of Africa (in Egypt) for the first time in 1989 [13]. Since then, recurrent LSD outbreaks have been reported in the Middle East [14]. From 2012 to 2014, the disease was disseminated in Lebanon, Turkey, Israel, Iraq, Jordan, Iran, Azerbaijan, and Cyprus [15]. From 2014 to 2015, the disease made its way from Asia to Europe [16]. Then, in 2015, the disease further spread in European countries, including Greece, Russia, Armenia, Azerbaijan, Albania, Bulgaria, Serbia, Montenegro, and Kosovo [14,16–19]. In 2016, numerous LSD outbreaks were found in southeast Europe. During 2019 to 2020, the disease became prevalent in many countries in Asia [20–25]. Currently, the disease is considered a major threat to the cattle industry and the livelihoods of cattle farmers in many regions of Asia. Since LSD outbreaks have been continuously reported on various continents with varying patterns, identifying trends and change points within those trends would enhance our understanding of this disease's epidemiology.

Change point analysis and trend analysis are statistical methods that are generally utilized to determine and monitor the behavior of time series data [26]. The term "change point" describes the time at which a change begins to occur. Change point analysis can detect abrupt or structural changes in time series data. For example, the number of LSD outbreak reports collected from the same country over a period (e.g., every month for many years) is considered time series data. Indeed, the number of LSD outbreak reports may be constant, change, or fluctuate from year to year or period to period (e.g., every 2–3 years). Accordingly, a small change in time series data may not be of much interest; however, a large or sudden change is worth investigating. Several studies have demonstrated the usefulness of change point analysis in detecting the change points of COVID-19 [26–28] and malaria [29].

Several research publications have provided critical information on the global status and regional or country situation of LSD outbreaks. For example, the spread of LSD from Africa to Europe, the Middle East, and Asia [30]; the epidemiology of LSD in Asia and Southeast Asian countries [31]; and the situation in specific regions [32] and countries, such as India [33] and Bangladesh [34], have all been described. However, only a few previous reports described the time series trend of LSD occurrences, and none of them investigated the significant change in the number of reports using time series change point detection methods. Additionally, studies on forecasting the number of LSD reports using time series models are very limited.

Disease forecasting utilizing well-accepted prediction methods is critical for developing strategic plans to monitor and prevent disease outbreaks. Predictions of COVID-19, which appeared in hundreds of publications, are a prime example of the widespread application of forecasting methodology [35,36]. Forecasts of infectious animal diseases are also demonstrated in numerous studies [37,38]. There are several forecasting techniques based on statistical frameworks and data-driven tools. In this study, we used auto-regressive moving average (ARIMA) and neural network auto-regressive (NNAR) models. ARIMA is a common classical statistical model, whereas NNAR is a method based on machine learning. These approaches are widely employed across numerous disciplines. Though various time series methods are available, the scope of this study is focused on ARIMA and NNAR.

Systematically, LSD outbreak reports from various regions around the globe have been published continuously by the WOAH. For a better understanding of LSD epidemiology, the trends, change points of disease trends, and forecasts of LSD outbreaks are worth investigating. Thus, the aims of this study were: (i) to determine the trends and change points in the time series data, and (ii) to forecast the number of LSD reports based on data from Africa, Europe, and Asia.

2. Materials and Methods

2.1. LSD Outbreak Data

In this study, data on the number of LSD reports in Africa, Europe, and Asia from January 2005 to January 2022, publicly available on the official WOAH website (https://wahis.woah.org, accessed on 14 August 2020), were imported and analyzed. Based on the WOAH report file, the numbers of LSD reports are shown as biannual data. For instance, 2020 has two semesters, with the first semester covering total LSD reports from January to June 2020, and the second semester covering July to December 2020.

2.2. Change Point Analysis

Change point analysis was applied to the data to determine significant changes in the number of LSD reports over time. A likelihood-based change point detection approach was utilized to detect changes in the mean and variance of the number of LSD reports. Because the number of LSD reports were count data, they are assumed to follow the Poisson distribution.

The *cpt.meanvar* function from the change point package detects changes in both mean and variance for four types of data distributions: exponential, gamma, Poisson, and normal. One of the major advantages of this function is its ability to detect multiple change points [39]. The use of this function has been demonstrated in several studies. The binary segmentation technique in *cpt.meanvar* was employed.

The binary segmentation technique estimates an approximate minimum of Equation (1). The *cpt.meanvar* algorithm first detects a single change point in the dataset. After determining the first change point, the data are divided into 2 subsegments at the change point location. The single change point process is repeated on the 2 datasets. If further change points are detected, the data is then split into further subsegments. This procedure is repeated until no change points are found in the subsegments [26,39].

Given m segments of the time series data, change point detection based on this technique is achieved by minimizing the function [39]:

$$\sum_{i=1}^{m+1}\left[C\left(x_{(t_{i-1}):t_i}\right)\right]+\beta f(m) \quad (1)$$

where C is a cost in function for a segment, and $\beta f(m)$ is a penalty to guard against overfitting.

2.3. Forecasting of LSD Outbreaks

The ARIMA and NNAR models were utilized to predict the number of LSD reports over the next 3 years (2022–2024) for each continent. The ARIMA technique is based on the principle that future values of a time series are generated from a linear function of past observations and white noise terms [40]. The ARIMA model is expressed by the following equations [41]:

$$y_t = \alpha + \phi_1 y_{t-1} + \phi_2 y_{t-2} + \cdots + \phi_p y_{t-p} + \varepsilon_t - \theta_1 \varepsilon_{t-1} - \theta_2 \varepsilon_{t-2} - \cdots - \theta_q \varepsilon_{t-q} \quad (2)$$

where y_t denotes the observed value at time t; α is a constant; $\phi_1, \phi_2, \ldots, \phi_p$ and $\theta_1, \theta_2, \ldots, \theta_q$ represent the autoregressive and moving average parameters, respectively; and ε_t is the value of the residual at time t.

ARIMA has three parameters, which can be written as ARIMA (p, d, q), where p, d, and q represent the order of autocorrelation, order of differencing, and order of moving average, respectively [42].

The NNAR model uses lagged values of the time series data as inputs to a neural network. For non-seasonal data, it has the notation NNAR (p, k), with p and k indicating the lagged inputs and nodes, respectively, in the hidden layer [42]. One of the main differences between ARIMA and NNAR is that the NNAR model does not require stationary values for forecasting [43].

The forecasting of LSD outbreak reports was carried out using R statistical software and the "dplyr", "xts", "tsbox", "TSstudio", and "forecast" packages. The *auto.arima* function performs 3 steps automatically: (i) data differencing until the data become stationary, (ii) examining ACF and PACF for the differenced data and selecting potential candidate models, and (iii) comparing the selected models using the Akaike information criterion (AIC) [42,44]. Technically, the results from all candidate models with their AIC are generated. The model with the lowest AIC is then considered the most suitable model (final model). Similarly, the *nnar* function, an automatic algorithm in the forecast package, provides a procedure to determine the best-fitting NNAR model as output [42].

Additionally, the African data were split into two datasets: one covering the years 2005–2015 (training set) and another covering the years 2016–2020 (validation set). The training set was used to build an ARIMA and NNAR model, both of which were utilized to generate forecast values. Further, the forecasted values were compared to the actual ones in the validation set. In addition, error metrics, including mean absolute percentage error (MAPE), mean absolute scale error (MASE), and root mean square error (RMSE), were calculated using functions from the "Metrics" package in order to measure the predictive abilities of the ARIMA and NNAR models [42,45].

3. Results

3.1. Lumpy Skin Disease Outbreak Reports

Overall, Africa had 29,966, Asia had 8837, and Europe had 2471 outbreak reports during the study period. Africa had an undulating trend during 2005–2019, and by the end of 2020, outbreaks had dropped sharply and remained consistently low, whereas Europe had a peak in 2016, a sharp decline in 2017, and then became stable, and Asia had three peaks throughout the period (Figure 1).

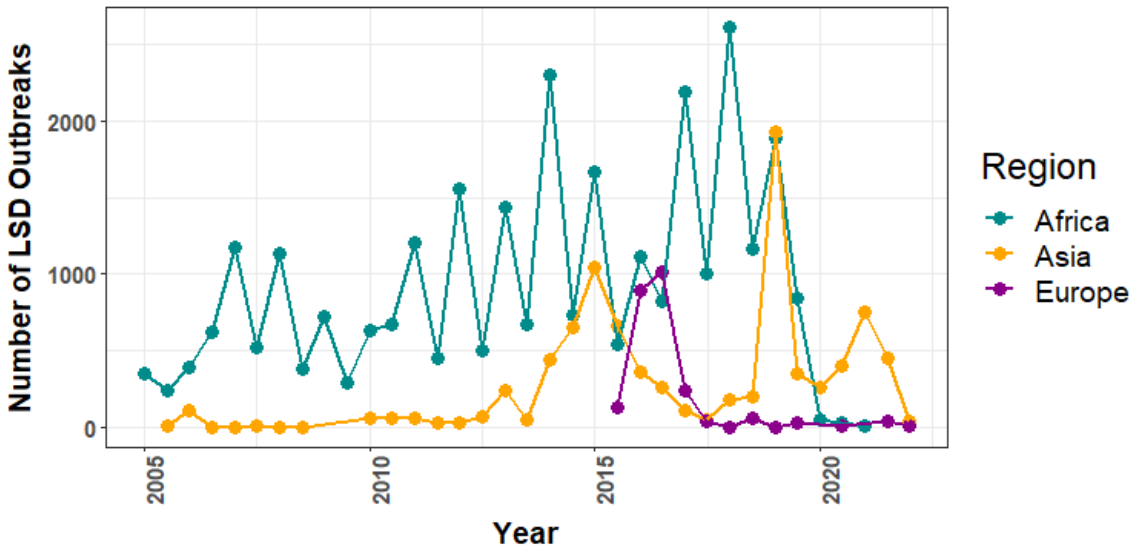

Figure 1. Overall trend of LSD outbreaks in Africa, Asia, and Europe from 2005 to 2020.

Regarding the top five African nations reporting the most LSD outbreaks (Figure 2), Zimbabwe consistently recorded outbreaks from 2005 to 2019, except 2006. Compared to other nations, Zimbabwe had the most recorded outbreaks (n = 18,072), with the highest number occurring in 2014 (n = 1915). Ethiopia, ranked second, has been reporting outbreaks for several years.

In Europe, Russia had the highest number of LSD outbreaks (n = 524), observed in 2016. North Macedonia, Albania, Montenegro, Russia, and Greece were the top five European nations to report LSD outbreaks that year (Figure 3). After the peak in 2016, the number of reports sharply dropped. From 2018 to 2022, Russia reported LSD outbreaks every year.

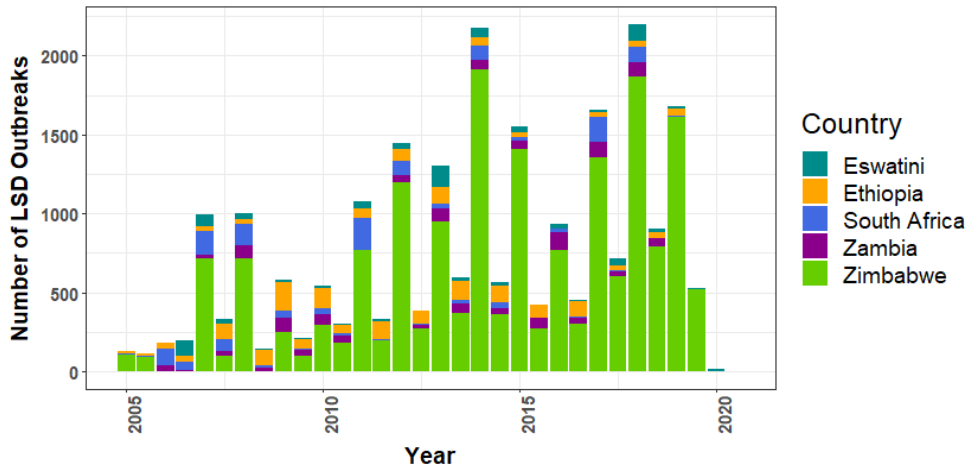

Figure 2. Top five African nations with the most reports of lumpy skin disease outbreaks.

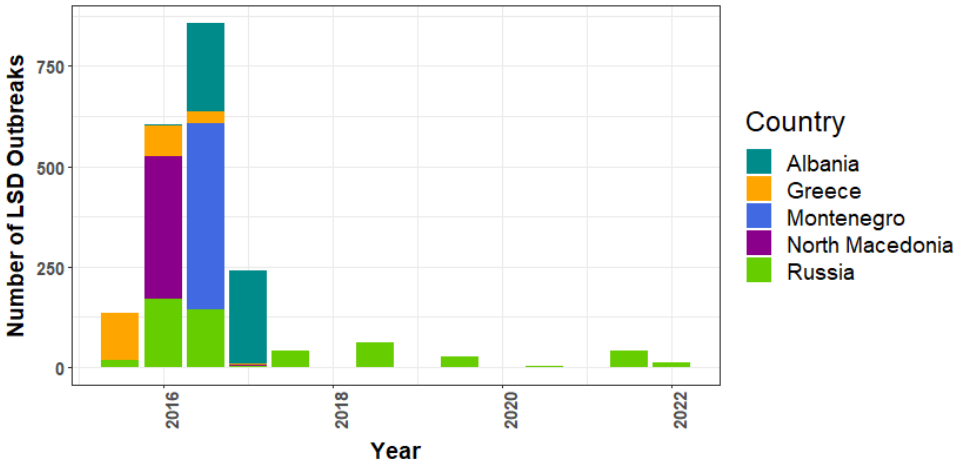

Figure 3. Top five European nations with the most reports of lumpy skin disease outbreaks.

In Asia (Figure 4), Oman had the highest number of reports (n = 1938) during the whole study period, with the maximum in 2019. From 2013 to 2019, Turkey reported notably high numbers of LSD epidemics in 2014 and 2015. Iran had its highest number in 2019. During the period from 2021 to January 2022, Thailand had the highest number of LSD reports.

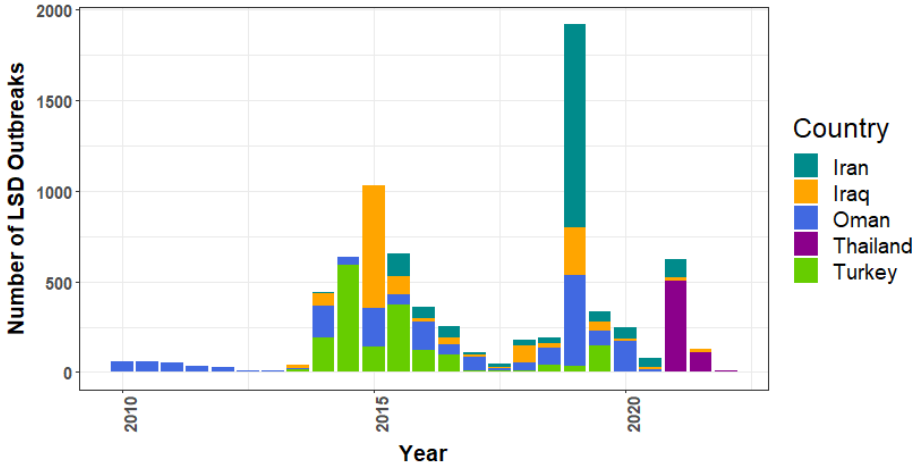

Figure 4. Top five Asian nations with the most reports of lumpy skin disease outbreaks. Notably, based on World Organization for Animal Health (WOAH) data, Turkey is categorized as part of Asia.

3.2. Change Points in the Time Series Data of Lumpy Skin Disease Outbreak Reports

The time-series data of the number of LSD reports have four change points for each continent. Technically, once the change points have been identified, the segments that correspond to them are represented. For example, the second segment is found between the first and second change points (Figure 5). In this study, each segment represents the mean of the number of LSD reports submitted during the period corresponding to that segment.

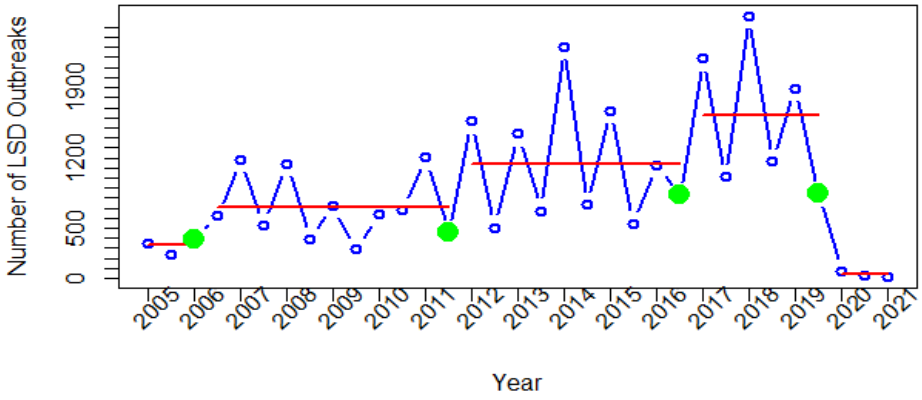

Figure 5. Change points in time series of LSD outbreak reports in Africa. Green dots are change points, and red lines are corresponding segments.

It was observed that the fourth segment of the African data (Figure 5) had the highest mean number of LSD reports compared to other segments. The fourth segment highlights the remarkably high number of reports during 2017–2019. Following the fourth change point, the number of LSD reports dropped sharply, and have remained stable since 2020.

For Europe, all four change points were detected during 2015–2017 (Figure 6). The first change point was identified in the second semester of 2015. The second change point was detected in 2016, when there was a significant increase in the number of LSD reports compared to the time of the first change point. From the third to fourth change points, a substantial decline in the number of LSD reports was seen. After the fourth detected change point in the first semester of 2017, the number of LSD reports remained stable since the second semester of that year.

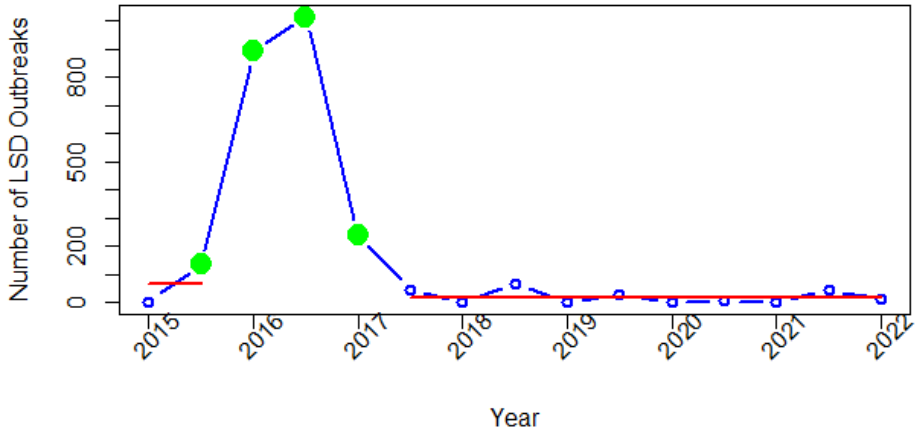

Figure 6. Change points in time series of LSD outbreak reports in Europe. Green dots are change points, and red lines are corresponding segments.

For Asia, four change points and five segments corresponding to them were identified (Figure 7). The first segment, from 2005 to 2013, displays a consistent pattern with a low number of outbreak reports. After the third detected change point in the second semester of 2018, the highest number of LSD outbreak reports was observed in the first semester of 2019. Then, the fourth change point was identified in the second semester of 2019.

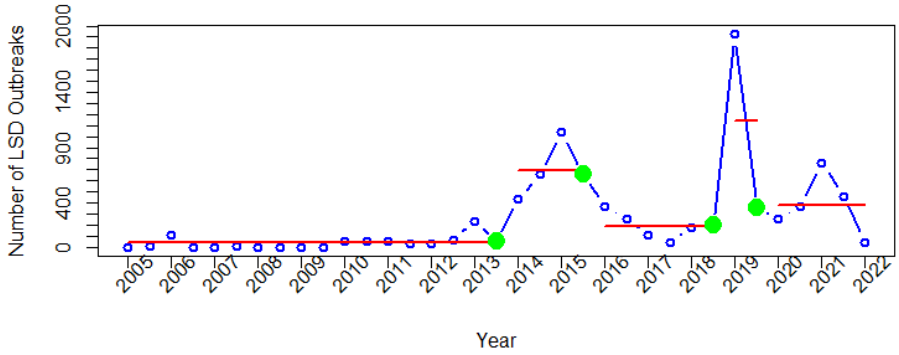

Figure 7. Change points in time series of LSD outbreak reports in Asia. Green dots are change points, and red lines are corresponding segments.

3.3. Forecasts of LSD Outbreaks

The forecasting of LSD outbreaks in Africa, Europe, and Asia by ARIMA and NNAR is shown in Figure 8. For Africa, both ARIMA and NNAR predict an increasing trend of LSD outbreaks, whereas for Europe, both models predict that outbreaks will stabilize. However, in Asia, ARIMA predicts a stable number of outbreaks, whereas NNAR predicts fluctuating outbreaks, which is approximately similar to the recent previous pattern. The most suitable models in ARIMA (p, d, q) and NNAR (p, k) notations obtained from the analysis are shown in Figure 8. Furthermore, the results showed that some NNAR forecast values were closer to actual values than ARIMA forecast values; nevertheless, some ARIMA forecast values were closer to actual values than NNAR forecast values (Figure 9). Moreover, the NNAR model yielded MAPE, MASE, and RMSE values of 4.48, 0.6, and 730.97, whereas the ARIMA model yielded 4.77, 0.63, and 726.94, respectively. These finding suggest that the predictive performances of both models were approximately comparable.

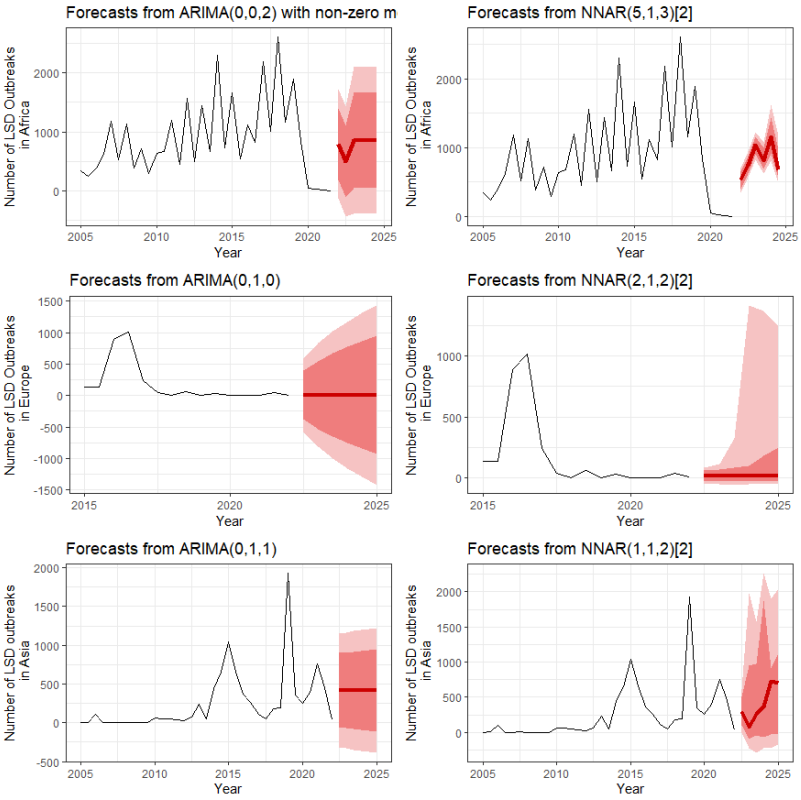

Figure 8. Number of LSD outbreaks in Africa, Europe, and Asia forecasted by ARIMA and NNAR. The thick red line represents point forecasts of LSD outbreak reports; the dark and light shades indicate 95% and 80% confidence intervals, respectively.

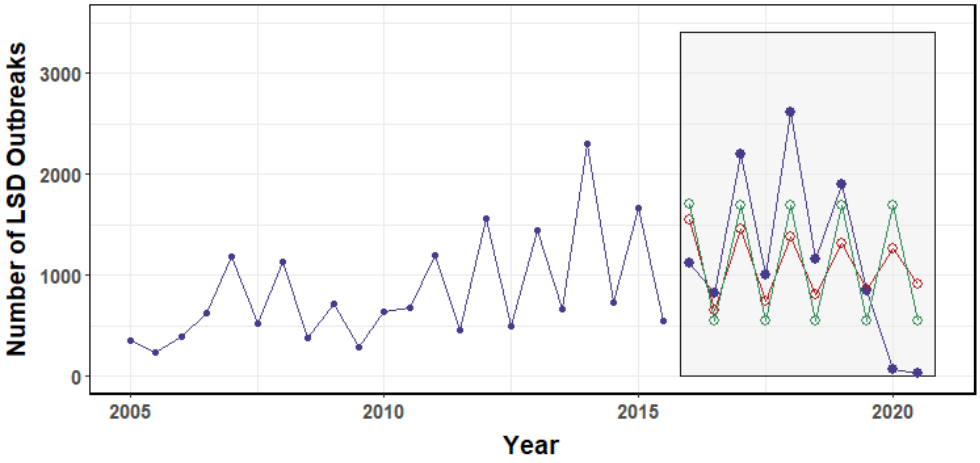

Figure 9. Report on the LSD outbreaks in Africa. The forecast models were built with data from 2005 to 2015, and validated with data from 2016 to 2022. The gray box represents the comparison between the forecasted LSD outbreak values obtained by the ARIMA (red circles) and NNAR (green circles) models and the actual outbreak values (blue dots).

4. Discussion

Change points in LSD outbreak time series data provide information on times when significant changes occurred in the data, which is essential information for epidemiology, particularly in the temporal dimension. Forecasts of the number of LSD reports based on well-accepted forecast methods offer useful baseline data that can assist authorities with planning disease surveillance and prevention efforts.

After the first outbreak in Zambia in 1929, the disease became prevalent in several regions of Africa [30]. Zimbabwe had the highest number of LSD reports throughout almost the entire study period (Figure 2). This finding may be due to land reform changes that muddled the distribution of cattle in Zimbabwe [46,47]. Ethiopia had the highest number of LSD reports, with a steady number throughout the period; all parts of the country suffered from disease except Dire Dawa and Harari [48]. Several outbreaks in Ethiopia were thought to be linked with vector population, dirty conditions on farms, improper vaccinations [49], movement of infected herds, and common water and grazing systems [48].

Our findings further show that the fourth segment (Figure 5) had the largest mean number of LSD outbreak reports when compared to other periods identified by change point analysis. In that year, outbreaks occurred in several African nations. For instance, a study in Ethiopia reported control efforts to limit LSD outbreaks in 2017 using vaccinations. Despite the use of the Kenya sheep pox virus vaccine (KS1 O-180) during that year, outbreaks continued to occur. It was suggested that the KS1 O-180 vaccine may be less efficient in controlling outbreaks [50]. As a result, it was shown that numerous outbreaks were reported from Ethiopia, which was related to the segment after the third change point mentioned above. Additionally, studies showed that numerous LSD outbreaks were observed in Egypt from 2016 to 2018 [51,52]. The risk factors associated with outbreaks in some regions of Egypt were comparable to those seen in Ethiopia, including shared water sources, animals being in contact with one another, and the introduction of new animals on farms [52]. It is intriguing that the number of outbreak reports has decreased dramatically since July 2019 (Figure 2), but, at present, no research has been conducted to clearly explain this phenomenon.

In Europe, four change points and only two segments were identified. These change points correspond to the situation of the disease in 2015–2016. The first change point was found in early 2015, when the first LSD outbreak occurred in Greece (Figures 3 and 6). The second change point represents a dramatically high number of LSD outbreak reports. The second and third change points correspond to the periods in 2016 when outbreak reports reached their second-highest and highest peaks. This change point may be due to the

spread of disease across the Balkan region [53]. During the same period, Turkey reported an LSD outbreak, and from there, the disease extended to Greece. Due to less vaccination coverage, the disease then spread to Bulgaria, Serbia, Macedonia, Montenegro, and Kosovo in 2016 [54]. Numerous LSD outbreaks in Eastern Europe were found to be associated with proximity to afflicted farms, high temperature, and an abundance of associated vectors [16]. It was noted that cross-border collaboration by veterinary authorities in several countries coordinated by the European Commission was the key to stopping the spread of the disease from 2015 to 2017 in southeast Europe [53]. No outbreaks were reported in southeast Europe in 2019 as a result of the region's mass immunization program, with more than 1.8 million cattle inoculated with homologous vaccines [55]. After the fourth detected change point in 2017, from the second semester of 2017 to January 2022, there were fewer than 200 LSD outbreak reports, and in this period, most of the reports were from Russia. Interestingly, it was noted that in 2015–2016, the outbreaks in Russia were solely attributed to LSDV field isolates, and in 2017, not only field LSDV strains, but also vaccine-like LSDV strains, caused several outbreaks. Further, the 2018 epidemic was mainly caused by recombinant vaccine-like isolates [56,57]. According to this finding, it was suggested that the use of live attenuated LSD vaccines in Kazakhstan, a country neighboring Russia, may have contributed to the invasion and spread of LSDV vaccine-like strains into Russia [56,57].

In Asia, Turkey reported numerous LSD outbreaks from 2013 to 2016 (Figure 4). The increasing trend of LSD in Turkey since 2013 has been previously described. In Turkey, despite the use of vaccines, the number of outbreaks increased, and then it was found that the Bakirkoy strain was inefficient in controlling LSD [13]. Later on, it was recommended to use a homologous vaccine [55,58]. When this type of vaccine was used, the number of outbreaks began to decline, and LSD was eventually eliminated from Turkey. It was suggested that the disease spread from Turkey to Iraq and Iran by crossing the borders [19,59], resulting in the highest outbreak being found in Iraq in 2019 [59]. In mid-July 2019, an LSD outbreak occurred in Bangladesh [60]. Soon after, the People's Republic of China reported an outbreak in the first week of August 2019. In the second week of August, an outbreak occurred in India. All of these outbreaks correspond well with the third and fourth change points, as well as the fourth segment. In 2020, countries, including Nepal, Sri Lanka, Bhutan, Vietnam, and Myanmar, reported LSD outbreaks to the WOAH [60]. Following the fourth change point, the fifth segment indicates a small increase in reports from 2020 to 2021. This finding indicates that Thailand had the highest number of LSD outbreak reports compared to other countries in Asia in 2021. Because it was the first time Thailand faced this threat, LSD outbreaks were found in cattle herds across the country, causing serious economic loss to the cattle industry [25,61].

In this study, we applied ARIMA and NNAR models to forecast the numbers of LSD outbreak reports. Overall, the number of outbreaks in Africa is expected to be higher than that reported in 2020–2021, whereas the number of outbreaks in Europe is projected to remain consistent. Forecasts of LSD outbreaks in Asia show an increasing trend in 2023–2024 based on the NNAR model, whereas ARIMA predicts a larger number of outbreaks than what occurred in January 2022. Notably, the results demonstrate that the prediction capabilities of both ARIMA and NNAR models tested with African data are not highly accurate, which may be influenced by the limited number of observations employed for model training, A follow-up study with more observations would allow for the development of more accurate forecast model models. Moreover, our results revealed that the prediction abilities of the ARIMA and NNAR were approximately comparable. This could be due to the fact that the data set contains both linear and non-linear patterns, and, therefore, the strengths of one model may not provide an advantage over another [37,45].

Our forecasts offer authorities useful information that can be incorporated into strategies to monitor and prevent future LSD outbreaks. Of note, the forecasts are generated from past observations; thus, they do not account for any future situation or implementation. If interventions such as more effective control measures are adopted, it is likely that fewer outbreak reports will be received than anticipated. In this aspect, we suggest using the

forecast numbers as basic information or benchmarks, with the goal of keeping the number of outbreaks below these figures.

The current study has several limitations. We were unable to determine the seasonality characteristics of the number of LSD outbreak reports due to the biannual format of the available data. Accordingly, it would be advantageous for future research if the data from WOAH were made public in a monthly format. Moreover, it important to note that forecast results should be interpreted with caution. Because forecasts are based on previous observations and patterns, some interventions and changes in disease drives in the future, which may change the patterns, will have an impact on the actual disease occurrences, and, therefore, our forecast may be over- or underestimated. Furthermore, there may be underreporting of LSD outbreaks in some countries during certain periods, so the reports used in this study may not represent the actual situation. Moreover, forecasting was limited to two methods. Thus, follow-up studies to investigate other methods of forecasting the number of LSD outbreak reports are warranted.

It is notable that LSDV isolates from outbreaks in some countries are genetically related [22,62,63]; therefore, international cooperation is critical to develop regional surveillance for monitoring, controlling, and preventing disease incursion. Such collaboration should also include sharing data regarding LSD outbreaks in each nation, such as epidemiological data and LSDV genetic information.

5. Conclusions

In this work, we used a statistical approach to identify major changes in the data underlying LSD outbreak reports. Additionally, we utilized time series models to forecast the number of LSD outbreak reports in Africa, Europe, and Asia during 2022–2024. Although LSD outbreak reports in Africa appear to be decreasing since 2020, it is expected that the number of reports will increase slightly. The number of LSD outbreak reports in Europe is projected to continue the previous 5-year steady trend. Additionally, the forecast predicts an increase in the number of outbreak reports in Asia. These findings indicate that LSD remains a substantial threat to the cattle industry in various countries; thus, efforts should be made to monitor its spread within and between regions. Additionally, because LSD is regarded as a significant transboundary disease, strict disease prevention and control in every country are critical. Furthermore, coordination among nations to control and eradicate the disease is essential.

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REVIEW

WILEY

Lumpy skin disease, an emerging transboundary viral disease: A review

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Abstract

Lumpy skin disease is an emerging bovine viral disease, which is endemic in most African countries and some Middle East ones, and the elevated risk of the spread of disease into the rest of Asia and Europe should be considered. The recent rapid spread of disease in currently disease-free countries indicates the importance of understanding the limitations and routes of distribution. The causative agent, Capripoxvirus, can also induce sheeppox and goatpox. The economic significance of these diseases is of great concern, given that they threaten international trade and could be used as economic bioterrorism agents. The distribution of capripoxviruses seems to be expanding due to limited access to effective vaccines and poverty within farming communities. This is largely due to the economic effects of the Covid-19 pandemic and the imposition of crippling sanctions in endemic regions, as well as an increase in the legal and illegal trade of live animals and animal products, and also global climate change. The present review is designed to provide existing information on the various aspects of the disease such as its clinicopathology, transmission, epidemiology, diagnosis, prevention and control measures, and the potential role of wildlife in the further spread of disease.

KEYWORDS

capripox, epidemiology, lumpy skin disease, transboundary disease

1 | INTRODUCTION

Lumpy skin disease (LSD), a major threat to stockbreeding, can cause acute or subacute disease in cattle and water buffalo (Givens, 2018; Tuppurainen, Venter, et al., 2017). All ages and breeds of cattle are affected, but especially the young and cattle in the peak of lactation (Tuppurainen et al., 2011). The reason why the World Organization for Animal Health (OIE) has placed this transboundary disease on the notifiable disease list is due to its significant economic losses and the potential for rapid spread (Tuppurainen & Oura, 2012). The recent spread of the disease in disease-free countries indicates the importance of its transmission, as well as control and eradication (Sprygin et al., 2019). Lumpy skin disease virus (LSDV) is a double-stranded DNA containing around 150 kilobase pairs (kbp) with relatively large sizes (230–260 nm), enclosed in a lipid envelope and belongs to genus Capripoxvirus, which is genetically related to the sheep pox (SPPV) and goat pox (GTPV) viruses (Bhanuprakash et al., 2006; Buller et al., 2005; Givens, 2018). This virus is the most economically significant in the Poxviridae family affecting domestic ruminants. The capsid or nucleocapsid of the virus is brick or oval shaped containing the genome and lateral bodies. Extensive DNA cross-hybridization between species causes serologic cross-reaction

and cross-protection among members. Although Capripoxviruses are generally considered to be host specific, SPPV and GTPV strains can naturally or experimentally cross-infect and cause disease in both host species. In contrast, LSDV can experimentally infect sheep and goats, but no natural infection of sheep and goats with LSDV has been reported.

2 | CLINICOPATHOLOGY

The clinical features of the disease include fever, inappetence, nasal discharge, salivation and lachrymation, enlarged lymph nodes, a considerable reduction in milk production, loss of body weight and sometimes death (Abutarbush et al., 2013; Annandale et al., 2014; Babiuk et al., 2008; Tasioudi et al., 2016). Furthermore, the disease is characterized by firm, slightly raised, circumscribed skin nodules (Figure 1) that are 2–7 cm in diameter and typically appear on the neck, legs, tail and back, shortly after the beginning of fever (Beard, 2016; Sevik & Dogan, 2017). The necrotic and ulcerative nodules raise the risk of myiasis (Beard, 2016). Oedema of the legs and lameness was observed in some cases (Tuppurainen & Oura, 2012). LSDV can lead to abortion (Radostitis et al., 2006), mastitis and orchitis (Awadin et al., 2011). However, nodules were not observed in aborted fetuses (Sevik & Dogan, 2017). With necropsy, lung oedema and congestion, nodules throughout the lungs and gastrointestinal tract were often observed (Zeynalova et al., 2016). Tissues such as the muzzle, nasal cavity, larynx, trachea, inside of the lips, dental pad, gingiva, abomasum, udder, teats, uterus, vagina and testes might be affected. The complications of severe disease were reported as keratitis, dysentery, lameness, pneumonia, mastitis and myiasis (Al-Salihi & Hassan, 2015; Tuppurainen et al., 2017).

The histopathological examination of skin nodules may reveal pathognomonic eosinophilic intracytoplasmic inclusion bodies in the keratinocytes, macrophages, endothelial cells and pericytes and are associated with the ballooning degeneration of spinosum cells.

FIGURE 1 Lumpy skin disease. Raised, circumscripted nodular lesions

Infiltration of the superficial dermal tissue of affected areas by inflammatory cells such as macrophages, lymphocytes and eosinophils is seen. In addition, widespread vasculitis and severe coagulative necrosis in subcutaneous muscles may be observed in some cases (Constable et al., 2017; Sevik et al., 2016). Pseudo-lumpy skin disease, urticaria, streptotrichosis (*Dermatophilus congolensis* infection), ringworm, *Hypoderma bovis* infection, photosensitization, bovine papular stomatitis, foot and mouth disease, bovine viral diarrhoea and malignant catarrhal fever are all considered in the differential diagnosis of LSD (Abutarbush, 2017).

3 | PATHOGENESIS

Following LSDV infection, virus replication, viremia, fever, cutaneous localization of the virus and development of nodules occur (Constable et al., 2017). Experimentally, after intradermal inoculation of the virus, the following events were reported:

- 4 to 7 days post-infection (DPI): localized swelling as 1–3 cm nodules or plaques at the site of inoculation
- 6 to 18 DPI: viremia and shedding of the virus via oral and nasal discharge
- 7 to 19 DPI: regional lymphadenopathy and development of generalized skin nodules
- 42 days after fever: presence of virus in semen (Coetzer, 2004).

Intracellular replication of the virus in fibroblasts, macrophages, pericytes and endothelial cells leads to vasculitis and lymphangitis in affected tissues (Coetzer, 2004).

It seems that young calves, lactating cows and underweight animals are more susceptible to natural infections, probably due to impairment of humoral immunity (Babiuk, Bowden, Boyle, et al., 2008). Animals that have recovered from natural infection by the virus have shown lifelong immunity. Calves from their infected dams are resistant to clinical disease for approximately 6 months because of the acquired maternal antibodies (Tuppurainen et al., 2005). Affected animals clear the infection and no carrier state has known for LSDV yet (Tuppurainen, Alexandrov, et al., 2017).

4 | TRANSMISSION

Lumpy skin disease can affect cattle, water buffalo and wild ruminants. It seems that sheep and goats are not infected by the virus (El-Nahas et al., 2011; Lamien, Le Goff, et al., 2011). LSDV can remain viable for long periods in the environment at ambient temperatures, especially in dried scabs. It is reported that the virus persists in necrotic skin nodules for up to 33 days or longer, in desiccated crusts for up to 35 days and for at least 18 days in air-dried hides. The virus can be inactivated at a temperature of 55°C for 2 hr and 65°C for 30 min (Mulatu & Feyisa, 2018). The main sources of infection are considered to be skin lesions as the virus persists in the lesions or scabs for long periods.

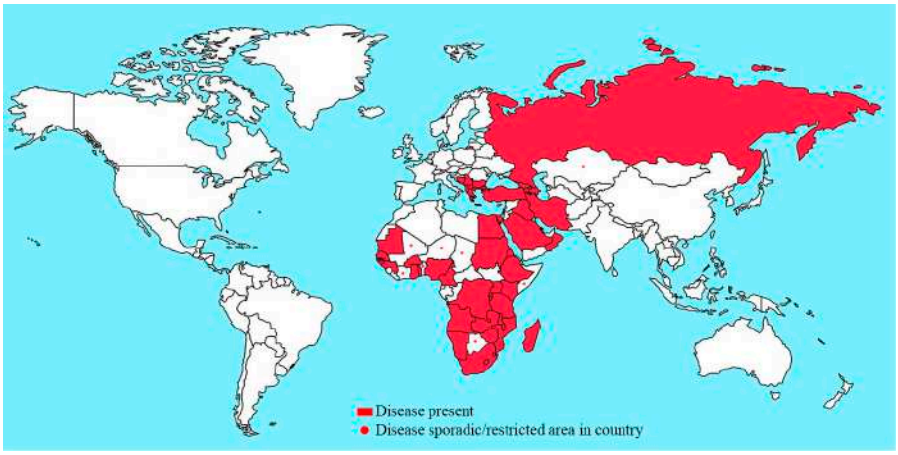

FIGURE 2 Global situation of lumpy skin disease (FAO, 2016)

The virus is also excreted via the blood, nasal and lachrymal secretions, saliva, semen and milk (transmissible to suckling calves).

The LSDV is transmitted through arthropods, particularly blood-sucking insects (Chihota, Rennie, Kitching, & Mellor, 2001, 2003; MacLachlan & Dubovi, 2011), contaminated feed and water and direct transmission in the later stages of the disease via saliva, nasal secretions and semen (Annandale et al., 2014; Chihota et al., 2001; Irons et al., 2005; Tuppurainen, Venter, et al., 2017). Some studies showed no positive correlation between cattle density and infection rates, indicating low importance of direct virus transmission, at least in the early stages of the disease, compared with the higher significance of indirect transmission (Carn & Kitching, 1995; Magori-Cohen et al., 2012).

As most LSD outbreaks have occurred in the summer when arthropods are most active, it may indicate the involvement of various vector species, especially blood-feeding insects, in virus spread (Kahana-Sutin et al., 2017; Sprygin et al., 2018).

Several studies have suggested a possible role of hard ticks in virus transmission (Lubinga et al., 2015; Tuppurainen et al., 2011, 2013). Lumpy skin disease virus and viral antigen were found in the saliva and the different organs of ticks, including the haemocytes, salivary glands and midgut in saliva and different organs of ticks such as haemocytes, salivary glands and midgut (Lubinga et al., 2013, 2014). Furthermore, the transstadial and mechanical transmission of the virus by ticks was proved based on molecular evidence (Tuppurainen & Oura, 2012). However, their prolonged attachment to the host does not explain the rapid occurrence of extensive epidemics. Therefore, it seems that ticks may be acting as reservoirs for the virus (Kahana-Sutin et al., 2017).

Aedes aegypti is the sole dipteran to be able to fully transmit the virus to susceptible cattle (Chihota et al., 2001). Mosquitoes such as *Culicoides nubeculosus*, *Culex quinquefasciatus* Say and *Anopheles stephensi* Liston were not able to transmit the virus (Chihota et al., 2003).

Although *Stomoxys calcitrans* has been seen in LSD outbreaks and has transmitted the capripox virus to sheep and goats (Baldacchino et al., 2013; Yeruham et al., 1995), the transmission of LSDV to susceptible animals has failed (Chihota et al., 2003). Since LSDV has been detected in *Culicoides punctatus*, it may play a role in virus transmission (Sevik & Dogan, 2017). It is also stated that the ratio of biting insects to host population is positively correlated with transmission possibility (Gubbins et al., 2008).

In experimental studies, the persistence of lumpy skin disease virus was indicated in bovine semen by both PCR and virus isolation (Annandale et al., 2010; Givens, 2018; Irons et al., 2005). Also, semen caused the transmission of the virus to inseminated heifers (Annandale et al., 2014).

5 | EPIDEMIOLOGY

5.1 | Geographical distribution

LSDV was diagnosed for the first time in Zambia in 1929 and then reported in several regions of African countries (Wainwright et al., 2013). The disease has been identified in Saudi Arabia, Lebanon, Jordan, Iraq, Israel, Turkey and Iran (Abutarbush et al., 2013; Al-Salihi & Hassan, 2015; Ben-Gera et al., 2015; Ince et al., 2016; Sameea Yousefi et al., 2017). Since 2015, it has spread to Russia, Azerbaijan, Armenia, Greece and Bulgaria, Albania, Kosovo, Serbia and Montenegro (Beard, 2016; EFSA, 2017; OIE, 2015; Ripani & Pacholek, 2015; Tasioudi et al., 2016; Wainwright et al., 2013; Zeynalova et al., 2016). Therefore, the elevated risk of the spread of disease into the rest of Europe and Asia should be considered (Figure 2).

The number of lumpy skin disease outbreaks in various countries was reported in the years 2014–2016 by the OIE (Figure 3). For instance, the numbers of LSD outbreaks in some Middle Eastern countries with extensive boundaries were 6, 8, 1,294, 1, 16, 1 and 330 in Iran, Iraq, Turkey, Kazakhstan, Azerbaijan, Armenia and Russia, respectively (OIE WAHID, 2018).

5.2 | Morbidity and mortality

There have been no reports on the incubation period of LSDV infection under field conditions (OIE, 2018). Although the morbidity rate

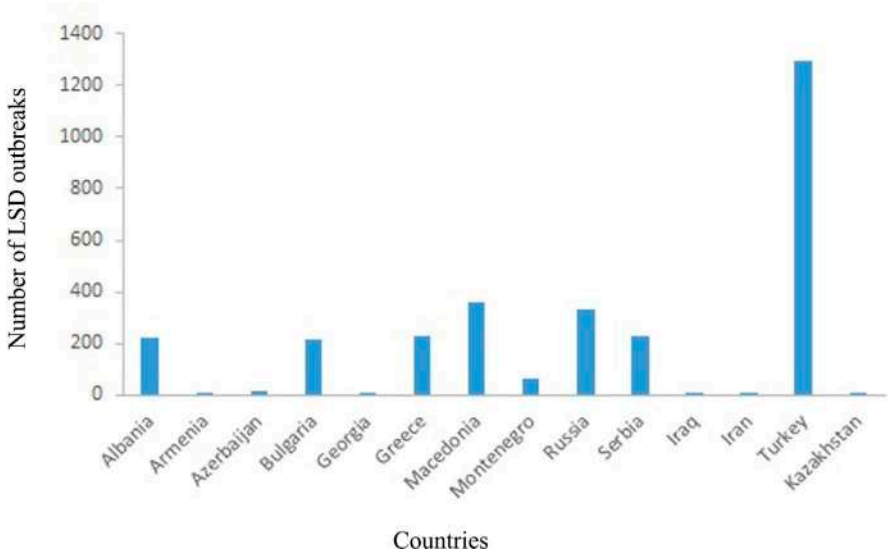

FIGURE 3 The number of LSD outbreaks in different countries during 2014–2016 (OIE, 2018)

varies between 5% and 45% (sometimes up to 100%), the mortality rate is usually under 10% (sometimes up to 40%) (Coetzer, 2004). For instance, the morbidity and mortality rates of outbreaks were reported as 8.7% and 0.4%, respectively, in Greece (Tasioudi et al., 2016) and 12.3% and 6.4%, in Turkey (Sevik & Dogan, 2017). The severity of the clinical disease is often influenced by the animal's age, breed, immune status and production period (Tuppurainen, Venter, et al., 2017).

5.3 | Risk factors

Risk factors associated with the spread of LSD include a warm and humid climate, conditions supporting an abundance of vector populations, such as those seen after seasonal rains, and the introduction of new animals to a herd.

The herd size, vector populations, distance to the lake, migration of herd, transport of infected animals into disease-free areas, common pasture and water sources have all been considered as other risk factors, which may increase the disease prevalence (Gari et al., 2010; Ince et al., 2016; Sevik & Dogan, 2017). Moreover, the direction and strength of the wind may likely contribute to the virus spread (Chihota et al., 2003; Rouby & Aboulsoud, 2016).

All ages and breeds of cattle, as well as both sexes, are susceptible to the disease (Tuppurainen et al., 2011). Also, risk factors associated with LSDV seropositivity include age, sex, management type, mean annual rainfall and common water source (Ochwo et al., 2019).

5.4 | Role of wildlife in the disease spread

Seropositivity can demonstrate the possible role of animals in the epidemiology of the disease (Barnard, 1997). It seems that mild clinical cases in wildlife are easily missed because it can be difficult or impossible to monitor the skin lesions (Barnard, 1997).

The susceptibility of springbok, impala and giraffe to the virus has been demonstrated (Lamien, Le Goff, et al., 2011; Le Goff et al., 2009; Young et al., 1970). Other species which have been seropositive for the virus include African buffaloes, blue wildebeest, eland, giraffe, impala and greater kudu (Barnard, 1997; Davies, 1982; Fagbo et al., 2014). The disease was reported in an Arabian oryx by Greth et al., (1992). However, the role of wildlife in the epidemiology of LSD is not yet well understood (Tuppurainen, Venter, et al., 2017).

6 | ECONOMIC IMPACT

Lumpy skin disease has led to serious economic losses in affected countries. The disease causes a considerable reduction in milk yield (from 10% to 85%) due to high fever and secondary mastitis. Other consequences of the disease include damaged hides, decline of the growth rate in beef cattle, temporary or permanent infertility, abortion, treatment and vaccination costs and death of infected animals (Alemayehu et al., 2013; Babiuk, Bowden, Boyle, et al., 2008; Sajid et al., 2012; Sevik & Dogan, 2017). The total cost of the LSD outbreaks in 393 surveyed herds was 822 940.7 GBP in Turkey (Sevik & Dogan, 2017). In Ethiopia, the estimated financial loss was 6.43 USD and 58 USD per head for local zebu and Holstein Friesian, respectively (Gari et al., 2010). Total production losses resulting from the disease have been estimated at 45%–65% in industrial cattle farming (Tuppurainen & Oura, 2012). The causative agent, capripoxvirus, can induce sheeppox and goatpox as well, and these diseases have economic significance, given that they present a major hindrance to international trade and may be abused as an economic bioterrorism agent.

TABLE 1 Different techniques for LSD diagnosis

Techniques	Purposes					
	Animals freedom from infection	Animal freedom from infection previous to movement	Contribution in eradication policies	Confirmation of clinical cases	Prevalence of infection surveillance	Immune status post-vaccination
Identification of agent						
Virus isolation	+	++	+	+++	+	-
PCR	++	+++	++	+++	+	-
Electron microscopy	-	-	-	+	-	-
Immune response detection						
Virus neutralization	++	++	++	++	++	++
Electron microscopy	+	+	+	+	+	+

Note: –: not appropriate for the purpose; +: may be used in some situations, but its application is limited by some factors such as reliability, cost, etc.; ++: appropriate method; +++: recommended method.
IFAT indicates Indirect Fluorescent Antibody Test; and PCR, polymerase chain reaction.

7 | DIAGNOSIS

Despite a primary clinical diagnosis of LSD, the diagnosis is confirmed by using conventional PCR (Orlova et al., 2006; Tuppurainen et al., 2005; Zheng et al., 2007) or real-time PCR techniques (Balinsky et al., 2008; Bowden et al., 2008). A real-time PCR technique has also been established, differentiating among LSDV, sheep and goat poxviruses (Lamien, Lelenta, et al., 2011). For differentiating virulent LSDV from the vaccine strain, Restriction Fragment Length Polymorphism (RFLP) has also been used (Menasherow et al., 2014). Furthermore, electron microscopy, virus isolation, virus neutralization and serological techniques have been utilized for LSDV detection as shown in Table 1 (OIE, 2018). It is stated that molecular methods are more precise, reliable and rapid compared with other methods (Stubbs et al., 2012). Among serological techniques, the virus neutralization test, which is slow and costly with a high specificity and low sensitivity, is the only currently validated/valid test (Beard, 2016). Babiuk, Bowden, Parkyn, et al. (2008) established immunohistochemical detection of LSDV antigen in an experimental study.

Despite the specificity and sensitivity of the western blot test, it is expensive and difficult to perform (OIE, 2018).

8 | PREVENTION AND CONTROL

The distribution of capripoxviruses seems to be expanding due to limited access to effective vaccines and poverty in farming communities in endemic regions, as well as the increased legal and illegal trading of live animals, besides global climate changes. Vaccination is the only effective method to control the disease in endemic areas along with movement restrictions and the removal of affected animals (Sevik & Dogan, 2017). The treatment of LSD is only symptomatic and targeted at preventing secondary bacterial complications using a combination of antimicrobials, anti-inflammatory, supportive therapy and anti-septic solutions (Salib & Osman, 2011). The culling of affected animals, movement restrictions and compulsory and consistent vaccination have been recommended as control strategies (Beard, 2016; OIE WAHIS, 2016; Tuppurainen, Venter, et al., 2017). However, regarding the role of arthropod vectors, elimination of the disease is likely to be difficult and any delays in the removal of infected animals increase the risk of LSD transmission (Tuppurainen, Venter, et al., 2017). Moreover, risk factors should be considered in control activities (Sevik & Dogan, 2017). Educating veterinarians and livestock workers would enable them to perform timely diagnoses of clinical cases, helping to slow the spread of disease (Beard, 2016).

Members of the capripoxvirus are known to provide cross-protection. Hence, homologous (Neethling LSDV strain) and heterologous (sheeppox or goatpox virus) live attenuated vaccines can all be used to protect cattle against LSD infection (OIE, 2013). In LSD-free countries that use the sheeppox vaccine to protect sheep against sheep pox, it was recommended to use the same vaccine during LSD outbreaks because of potential safety issues associated with

the live attenuated LSDV vaccine use (Tuppurainen & Oura, 2012). Furthermore, the rapid confirmation of a clinical diagnosis is essential so that eradication measures, such as quarantine, slaughter-out of affected and in-contact animals, proper disposal of carcasses, cleaning and disinfection of the premises, and insect control can be implemented as soon as possible during the eruption (Constable et al., 2017; Tuppurainen et al., 2005). Moreover, rigorous import restrictions on livestock, carcasses, hides and semen from endemic areas must be in place in disease-free areas (Sevik & Dogan, 2017).

It is known that complete immunity against LSD was not provided by used sheep pox vaccines (Brenner et al., 2009). Nevertheless, they are used in some countries such as Iraq, Iran, Turkey and African countries with overlap between LSD, SPP and GTP (Sameea Yousefi et al., 2017).

The commercially accessible vaccines against LSD are live attenuated vaccines. Although cutaneous lesions have developed in some vaccinated animals after exposure to the virus, there were a greater amount of clinical cases in unvaccinated flock compared with vaccinated flock (Brenner et al., 2009; Stram et al., 2008). These cheap vaccines can give adequate protection through annual vaccination programmes (Tuppurainen, Venter, et al., 2017). Currently, the safety and efficacy of a newly developed inactivated vaccine have been confirmed in a field study by Hamdi et al. (2020).

Live vaccines produce a strong and long-lasting immune response, and are efficient in the control of disease spread (Tuppurainen et al., 2020). However, live vaccines can cause local inflammation and a mild disease with skin lesions (Bedekovic et al., 2017). Although inactivated vaccines are costly and need several administrations, they are safe and it is possible to combine them with other antigens to make polyvalent vaccines that could be used in disease-free countries. Moreover, inactivated vaccines could be applied in the final stage of disease eradication as a part of the strategy that uses live vaccines first (Hamdi et al., 2020).

As there is a chance of recombination between the wild field strain and the live vaccine, the risk of coinfection should be considered with the use of live vaccines (Sprygin et al., 2018). Natural infection is probably made worse by the vaccination of infected animals (Sprygin et al., 2019). Also, these vaccines are not recommended in disease-free countries. A differentiating infected from vaccinated animals (DIVA) should be developed for non-endemic countries, this would also be an effective tool for endemic countries (Tuppurainen, Venter, et al., 2017).

9 | CONCLUSIONS

The recent spread of the disease into disease-free areas indicates its epidemiological and economic significance. Considering the extensive boundaries of Middle East countries, animal movements among these countries should be attentively controlled by veterinary authorities. Furthermore, paying close attention to the different aspects of the disease, such as transmission and epidemiology, and the implementation of effective preventive measures such as vaccination, could result in better disease control. Therefore, accurate and timely diagnosis in endemic areas, vaccination with the homologous strain of the LSDV, vector control, animal movement restriction and LSDV testing of bulls used for breeding are highly recommended as tools to control further spread.

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CONFLICT OF INTEREST

The authors declare that there was no conflict of interest.

Peer Review

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Review Article

Lumpy Skin disease: Review of literature

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Abstract

Lumpy skin disease (LSD) causes huge economic losses in the livestock industry. It is caused by Lumpy skin disease virus (LSDV), which belongs to the family Poxviridae, with the Neethling strain the prototype. LSDV belongs to the genus Capripoxvirus that includes sheep pox virus and goat pox virus. LSD is an enzootic infectious, eruptive and seldom fatal disease of cattle characterised by nodules on the skin. Cattle and water buffalo are the only animal species affected, with high morbidity rate, but low mortality, however, death rates are higher among calves. LSD causes loss of milk and beef production, abortions in females and sterility in males. The original foci of LSD are from Zambia in 1929. LSD is considered as an endemic disease in the African continent. However, the disease has been moved beyond Africa in 1984. It is reported in Madagascar and some countries in the Arab Gulf Peninsula and Middle East. Recently, the disease is reported in LSD free countries (Jordan, Syria, Lebanon, Turkey, Iran and Iraq) with potential economic loss to the livestock industry. This review article intends to discuss the LSD in the light of the recent situation raises concerns the spreading of the disease in LSD free countries.

Keywords: Lumpy skin disease, cow, knopvelsiekte, Middle East.

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Introduction

Lumpy skin disease (LSD, Pseudo-urticaria, Neethling virus disease, exanthema nodularis bovis, and knopvelsiekte) is an infectious disease. It is caused by a virus (LSDV) in the family Poxviridae, genus Capripoxvirus. It is closely related antigenically to sheep and goat pox virus. However, these viruses cannot be differentiated using routine serological test (Alexander *et al* 1957). LSD is a disease of cattle and water buffalo. It is a vector-borne disease transmitted by different biting and biting blood-feeding arthropods. LSD Causes considerable economic losses due to emaciation, damage to hides, infertility, mastitis, loss of milk production, and mortality of up to 20%. The severity of clinical signs of LSD depends on the strain of capripoxvirus and the host cattle breed (Anonymous 1988). Until 1989, Lumpy skin disease is limited to

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African continent. However, the disease is moved outside Africa to Madagascar and the Middle East and causes serious economic loss to the livestock industry. The incubation period in the field is believed to be two to five weeks, and lesions first appear at the inoculation site in 4 to 20 days. Fever is the initial sign that is followed within two days by the development of nodules on the skin and mucous membranes (Tuppurainen and Oura 2012; Brenner *et al* 2006). A diagnosis of LSD is building upon the basis of the typical clinical patterns (morbidity and mortality). A confirmed diagnosis is based on transmission electron microscopic (TEM), immunoperoxidase (IMP) staining, antigen-trapping enzyme-linked immunosorbent assay (ELISA) and a polymerase chain reaction (PCR) test. There is no specific treatment for LSD. However, supportive treatment should be given to infected animals to relieve clinical signs and to control all secondary complications. Immunization of the susceptible animals is the effective methods to control the disease in South Africa, and the effective vaccines are produced from the Neethling strain virus (Ayelet *et al* 2014).

The Causative Organism

The genus Capripoxvirus of the family Poxviridae is the causative agent of Lumpy skin disease. Lumpy skin disease virus (LSDV) is closely related antigenically to sheep and goat poxviruses (Woods 1988). Although these three viruses are distinct, they cannot be differentiated with routine serological tests (Figure 1). LSDV is susceptible to 55°C/2 hours and 65°C/30 minutes. It can be recovered from skin nodules and kept at –80 °C for 10 years. The infected tissue culture fluid can be stored at 4°C for 6 months. The virus is susceptible to highly alkaline or acid pH. However, there is no significant reduction in titre when held at pH 6.6–8.6 for 5 days at 37°C. LSDV is susceptible to ether (20%), chloroform, formalin (1%), and some detergents, e.g. sodium dodecyl sulphate. In addition, it is also susceptible to phenol (2% /15 minutes), sodium hypochlorite (2–3%), iodine compounds (1:33 dilution), Virkon® (2%) and quarternary ammonium compounds (0.5%). LSDV has remarkably stable, surviving for long periods at ambient temperature, especially in dried scabs. LSDV is very resistant to inactivation. It is surviving in necrotic skin nodules for up to 33 days or longer, desiccated crusts for up to 35 days and at least 18 days in air-dried hides. It can remain viable for long periods in the environment. Meanwhile, the virus is susceptible to sunlight and detergents containing lipid solvents, while, in dark environmental conditions, such as contaminated animal sheds, it can persist for many months. The genomic sequence of LSDV is identified (Tulman *et al* 2001). The LSDV genome (151-kbp) consists of a central coding region bounded by identical 2.4 kbp-inverted terminal repeats and contains 156 putative genes. However, the chordopoxviruses of other genera reveals 146 conserved genes, which encode proteins involved in transcription and mRNA biogenesis, nucleotide metabolism, DNA replication, protein processing, virion structure and assembly, and viral virulence and host range. LSDV genes share a high degree of colinearity and amino acid identity (average of 65%) of its genomic region with genes of other known mammalian poxviruses, particularly suipoxvirus, yatapoxvirus, and leporipoxviruses. The colinearity is disrupted and poxvirus homologues are either absent or share a lower percentage of amino acid identity (average of 43%) in the terminal regions. Although LSDV resembles leporipoxviruses in gene content and organization, it also contains homologues of interleukin-10 (IL-10), IL-1 binding proteins, G protein-coupled CC chemokine receptor, and epidermal growth factor-like

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protein which are found in other poxvirus genera. LSDV is closely related to other members of the Chordopoxvirinae, it contains a unique complement of genes responsible for viral host range and virulence. The complete genome sequences of several capripoxviruses, including LSDV (Tulman *et al* 2001), sheep poxvirus and goat poxvirus (Tulman *et al* 2002), have been published.

History of lumpy skin disease

The first description of the clinical signs of LSD was in 1929 in Zambia (formerly Northern Rhodesia) (Morris 1931). In the beginning, LSD signs were considered to be the consequence either of poisoning or a hypersensitivity to insect bites. Same clinical signs were occurred in Botswana, Zimbabwe and the Republic of South Africa between 1943 and 1945, where the infectious nature of the disease was recognized in these outbreaks.

In South Africa, LSD occurred as a panzootic, which affected eight million cattle. The disease continuous until 1949, and generate massive economic losses (Thomas and Mare 1945; Von Backstrom, 1945; Diesel, 1949). In 1957, LSD was identified in East Africa in Kenya. In 1972, the disease was reported in Sudan (Ali and Obeid 1977) and West Africa in 1974. While, it was spreading into Somalia in 1983 (Davies 1991 a and b).

The disease has continuous to spread over most of African continent in a series of epizootics as previously recorded by Davies (1991 b) and House (1990). In 2001, LSD was reported in Mauritius, Mozambique and Senegal.

Nowadays, LSD occurs in most of African continent (except Libya, Algeria, Morocco and Tunisia) (Tuppurainen and Oura 2012). Until 1980s (From 1929 to 1984) the disease was limited to countries in Sub-Saharan African continent, albeit it's probable to move beyond this range had been proposed (Davies 1981).

In the Middle East, the outbreaks of the LSD, were reported in Oman in 1984 and 2009 (House *et al* 1990; Kumar 2011; Tageldin 2014). Kuwait in 1986 and 1991, Egypt in 1988 and 2006 (Ali *et al* 1990; House *et al* 1990; Davies 1991a; Fayez and Ahmed 2011; Ali and Amina 2013), Israel in 1989 and 2006 (Shimshony 1989; APHIS 2006; Shimshony and Economides 2006), Bahrain in 1993 and 2002-2003, Yemen, United Arab Emirates in 2000 and the West Bank also reported LSD invasion (Shimshony and Economides, 2006; Kumar 2011; Sherrylin *et al* 2013). In Oman, LSD was re-emerged once again in 2009 in a farm population of 3200 Holstein animals with 9 high morbidity and mortality rates 30-45 % and 12% respectively (Tageldin *et al* 2014). In Egypt, Suez Governorate, the LSD was reported in May 1988 (Ali *et al* 1990). The disease was arrived in Egypt with cattle imported from-Africa and kept at the local quarantine station. It spread locally in the summer of 1988 and apparently overwintered with little or no manifestation of clinical disease. Twenty-two out of twenty-six Egyptian governorates were affected with diseases, then the disease reappeared in the summer of 1989 and continuous for five to six months. This epizootic showed low morbidity rate (2%) due to the vaccination procedure that included nearly two million cattle with a sheep pox vaccine. However, approximately 1449 animals died. In the summer of 2006, in one farm with a total of 30 cases in dairy cows. LSD outbreak was re-emerged once again in several Egyptian governorates, where all age groups and both sex of Egyptian cattle were infected with severe and serious complications. (Fayez and Ahmed 2011; Ali and Amina 2013). In Israel, the LSD was reported in 1989. This outbreak was

ISSN 2307-8073

subsequently disposed of by the slaughter of all infected cattle as well as contacts. In addition, ring vaccination with a sheep pox strain was carried out around the focus area which led to limit the distribution of the disease.

One of the recent outbreaks of LSD in African continent were occurred in central Ethiopia in 2007 to 2011. These outbreaks were described as active. It was investigated in four districts: Adama, Wenji, Mojo and Welenchiti. The totally 1,675 outbreaks were reported over 5 years period from 2007 to 2011, with 62,176 cases and 4,372 deaths. The Oromia represented the highest numbers of outbreaks (1,066), followed by Amhara (365) and the Southern Nations, Nationalities and People's Region (123). The 2010 were reported the highest number of outbreaks that were frequently seen between September and December. The morbidity and mortality rates were 13.61% (296) and 4.97 % respectively (Ayelet *et al* 2014).

Syria, Lebanon and Jordan are joined LSD affected countries in 2012 and 2013. The disease has been reported in Turkey in October 2013, Iran and Iraq in 2014 (Figure 2) (Sherrylin *et al* 2013; Lumpy skin disease, Iraq 2015).

In Jordan, LSD was reported as emerging disease. The outbreak started in mid-April, 2013. Two adult dairy cattle in Bani Kenanah district, Irbid governorate, on the Jordanian border of Israel and Syria, were developed clinical signs suggestive of LSD and confirmed as positive by PCR. The overall morbidity rate was 26%, mortality rate 1.9% and case fatality rate 7.5% (Abutarbush *et al* 2013).

In Iran, the LSD considered as emerging disease that has been identified for the first time in 2014. In total, six cases were reported in dairy cows. The outbreaks were reported in two villages in the west of the country. The illegal movement of animals and the usual vectors are thought to be the source of the outbreak. (The cattle site 2014).

The expectation of the travelling and invasion of the LSD to free neighbours countries are possible. LSD may invade north and west from Turkey into Europe and the Caucasus and East to Central and South Asia. In addition, Russian Federation to the north and Bulgaria and Greece to the west are considered to be at-risk countries.

Figure 1. Classification of Lumpy skin disease virus

ISSN 2307-8073

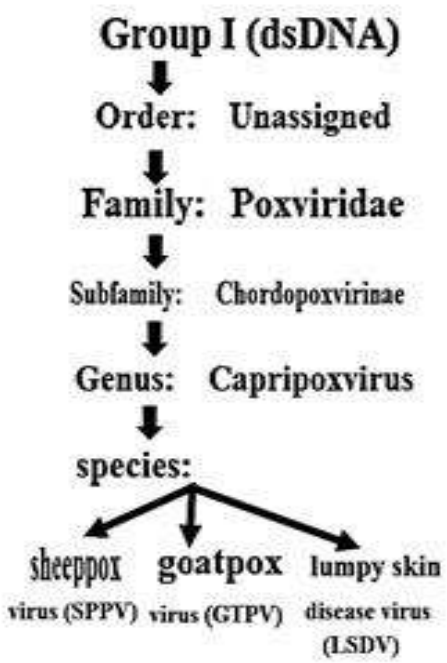
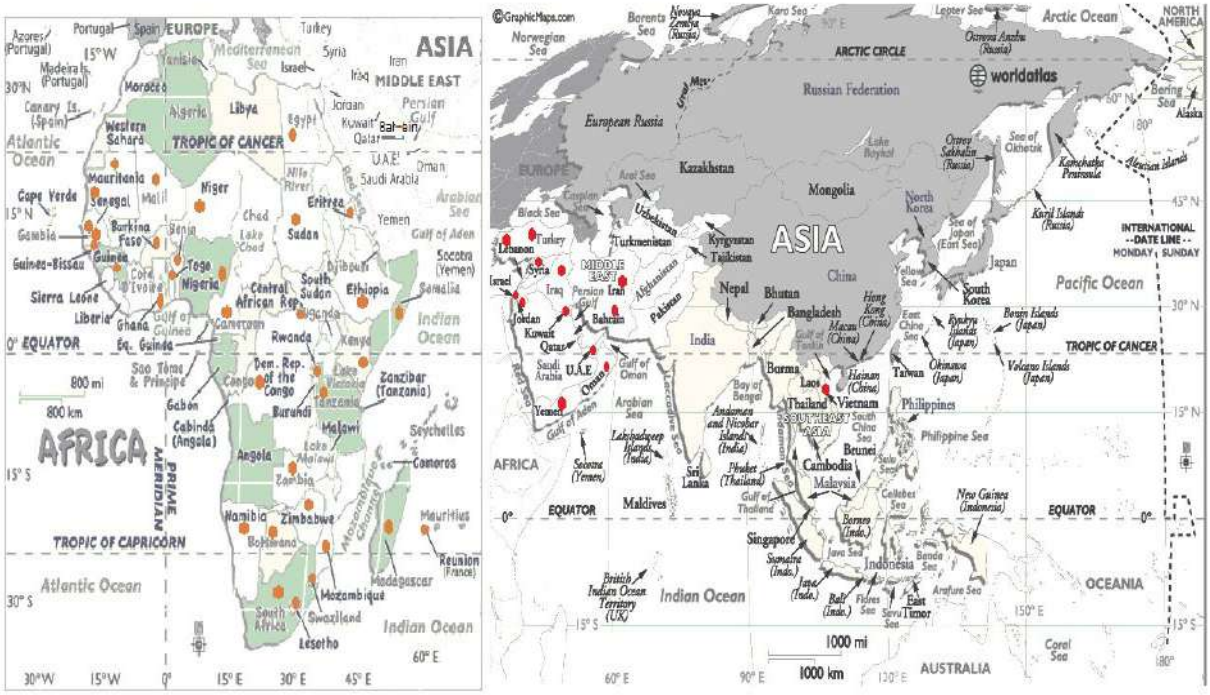


Figure 2. Map of Lumpy skin disease distribution (The red dots show the emergence foci of the disease)



Epidemiology

A. Morbidity and mortality rates

ISSN 2307-8073

There is gigantic variation in the morbidity and mortality rates of LSD outbreaks. It depends on these factors: geographic location and climate; the management conditions; the nutritional status and general condition of the animal; breed of cattle affected; immune status; population levels and dissemination of putative insect vectors in the various habitats; virus virulence. The morbidity rate for LSD are ranges from 5 to 45%. However, the morbidity rates of 1 to 5 percent is considered more usual. Higher rates have been encountered in epizootics in Southern, West and East Africa and the Sudan although so far much lower rates may occur during the same epizootic. In addition, high morbidity and mortality rates 30-45 % and 12% respectively were also reported in Oman in 2009 in a farm population of Holstein cattle (Sherrylin *et al* 2013).

B. Susceptible animals

LSD has a narrow vertebrate host range. Cattle and Buffalo are the species, which become infected naturally during field outbreaks. Five occurrences of clinical cases of LSD in Bubalus bubalis, the Asian water buffalo have been reported (Ali *et al* 1990). No other domestic ruminant species becomes infected naturally during field outbreaks. All cattle breeds appear to be equally susceptible to the disease. However, some other researcher found that imported breeds with thin skins, such as Bos taurus, Friesland cattle and the Channel Island breeds, were far more susceptible than indigenous breeds with thicker skins, such as the Afrikaner and Afrikaner cross- breeds. Young calves are more susceptible to the disease and may develop the characteristic lesion within 24 to 48 hours, although all ages groups of animals are susceptible. A single clinical case of a Capripox infection, probably LSD, was described in an Arabian oryx in a zoo in Saudi Arabia. (Greth *et al* 1992). Experimental inoculation of some wild species such as: impala (Aepyceros melampus), Thomsons gazelle (Gazella thomsonii) and the giraffe (Giraffa camelopardalis), was followed by the development of LSD lesions in the skin (Young *et al* 1968).

C. Transmission

The transmission of lumpy skin disease virus has not fully understood (Weiss 1968; Kitching and Mellor 1986; Carn and Kitching 1995). The mechanical spread of the LSD virus has mainly associated with flying insects and all the possible clue confirms the field observations that epidemics of LSD occur at periods of greatest biting insect activity. Most cases are believed to be resulted from the transmission by an arthropod vector. There are variations in the attack rates from 10-15% to nearly 100% in different epidemics due to the differences in the active vector species that found in different situations. Stomoxys, the tabanids and tsetse flies, are likely to be doubtful in dry conditions and related to lower levels of transmission. However, huge mosquito-breeding sites are common in very high morbidity rates that occur after rain.

Lubinga (2014), has been found three blood sucking hard tick species, which involved in the transmission of LSDV in sub-Saharan Africa. The three tick species identified as vectors of the disease are the Rhipicephalus (Boophilus) decoloratus (blue tick), R. appendiculatus (brown ear tick) and Amblyomma hebraeum (bont tick). Lubinga's study has confirmed that ticks are acted as vectors for the virus. Lubinga stated: "The ticks also act as 'reservoirs' for the virus, as it can persist in these external parasites during periods between epidemics "The virus has been found in their saliva and organs and

ISSN 2307-8073

could potentially overwinter in these ticks. Lubinga mentioned that ticks can be spread over long distances by moving along with their animal host, for instance, while feeding on migrating birds, and the change of climate due to global warming is making it possible for ticks to survive successfully and quest in areas where previously they could not survive due to very cold conditions. Same evidence has been published and reporting a possible role for hard ticks in the transmission of LSDV (Tuppurainen et al., 2011). The study showed molecular evidence of transstadial and transovarial transmission of LSDV by Rhipicephalus (Boophilus) decoloratus ticks, and mechanical or intrastadial transmission by Rhipicephalus appendiculatus and Amblyomma hebraeum ticks.

LSD virus has been isolated from Stomoxys calcitrans and Musca confiscata and transmitted experimentally using S. calcitrans but other vectors are also doubtful including Biomyia, Culicoides, Glossina and Musca spp. However, in a recent study, despite the detection of virus in mosquitoes (Anopheles stephensi, Culex quinquefascuatus) the stable fly and a biting midge (Culicoides nebeculosis) after they had fed on cattle with lumpy skin disease, the infection did not transmit to susceptible cattle when these arthropods were allowed to re-feed on them.

Cattle can be infected by drinking water, although ingestion and direct contact transmission are not common routes, even though the virus is present in nasal and lacrimal secretions, semen, and milk of infected animals. Transmission of LSDV through semen (natural mating or artificial insemination) has not been experimentally demonstrated, but LSDV has been isolated in the semen of experimentally infected bulls.

Intra-uterine infection is assumed, which is supported by the presence of extensive skin lesions in the aborted calves (Weiss 1968; Irons *et al* 2005). Some wild species (giraffe, impala, and Thomson's gazelle) have been infected by parenteral inoculation with LSD virus and have developed characteristic lesions. Lesions of LSD have not been seen on these animals, when they have been present during epizootics of the disease. Sheep and goats do not become infected during outbreaks of LSD even when held in close contact with infected cattle. African buffaloes (Syncerus caffer) do not show lesions in the field during epizootics of LSD, and nor did the majority of Asian water buffaloes, Bubalus bubalis, exposed during the Egyptian LSD epizootic. Five cases of LSD-like lesions in buffaloes were reported in Egypt. Both buffalo types may suffer an inapparent infection and seroconvert. While infection by contact can occur, this is thought to occur only at a low rate and is not considered a major component of transmission during epizootics. The movement of animals from infected herds, often months after recovery, has regularly resulted in the introduction of infection. The source of the virus is considered to be from old skin lesions. In most of Sub-Saharan Africa, the disease has been observed to appear following the seasonal rains. There is always an increase in the population of different arthropod species. Local movement of the disease in the presence of strict quarantines has been attributed to aerial movement of insect vectors in low-level air currents. The onset of frosts in South Africa and Egypt results in a great fall in the number of cases of LSD, which virtually disappears over the winter season to reappear again in the spring and summer. The disease spread throughout Egypt in the summer of 1989, despite total restrictions on animal movements. A focus of LSD appeared in Israel some 80-200 km distant from active foci of LSD transmission in Egypt, this suggests that aerial movement of biting insects had occurred. The imposition of quarantines does prevent the spread of infection by recovered animals but not by the aerial movement of vectors (Fayez and Ahmed 2011).

ISSN 2307-8073

Direct contact is considered to be an ineffective means of transmission. Communal cattle grazing and watering points have been associated with the occurrence of LSD. Transmission of LSDV through semen (natural mating or artificial insemination) has not been experimentally demonstrated, but LSDV has been isolated in the semen of experimentally infected bulls (Weiss 1968; Irons *et al* 2005).

Pathogenesis

Intravenous, intradermal and subcutaneous routes are used in experimental infection. The intravenous route develops severe generalized infection, while the intraepidermal inoculation develops only 40% to 50% of animals may developed localized lesions or no apparent disease at all. A localized swelling at the site of inoculation after four to seven days and enlargement of the regional lymph nodes, develop after subcutaneous or intradermal inoculation of cattle with LSDV (Vorster and Mapham 2008). However, generalized eruption of skin nodules usually occurs seven to 19 days after inoculation. LSDV replicates inside the host cells such as macrophages, fibroblasts, pericytes and endothelial cell in the lymphatics and blood vessels walls lead to developing vasculitis and lymphangitis, while thrombosis and infarction may developed in severe cases. Viraemia occurred after the initial febrile reaction and persisted for two weeks. In natural infection, very young calves, lactating cows, and malnourished animals seem to develop more severe disease that may be due to an impaired humoral immunity. A lifelong cell- mediated immunity is developed in most animals that recover from clinical disease. Calves are born from the infected cow acquire maternal antibodies that may protect them from clinical diseases for approximately six months. LSDV was demonstrated in saliva at least for 11 days after the development of fever, in semen for 42 days and in skin nodules for 39 days, from experimentally infected cattle.

Clinical signs

The clinical signs of LSD have two febrile phases (biphasic fever), which is appeared after variant incubation period 4-12 days (usually 7 days). The temperature of the infected animals raises to 40-41.5°C, which may persist for 6-72 h or more and may rarely be up to10 days. The infected animals also show lacrimation, increased nasal and pharyngeal secretions, anorexia, dysgalactia, general depression and a disinclination to move. The initial clinical signs of LSD are varied in severity that depends on the management system of the herd but do not relate to animal sex or age.
Multiple firm circumscribed nodules are developed in the skin of the animals. These nodules are suddenly erupted within 1-2 days. The erupted nodules may be widespread or restricted to just a few lesions. The head, neck, the perineum, the genitalia, udder, and the limbs are the predilection sites. The whole of the skin of the infected animal is covered with lesions infrequent cases. Typical LSD lesions are round, irregular, about 5-50 mm in diameter, and appear as circumscribed areas of erect hair over a firm and slightly raised area of skin (Figure 3). The healthy skin is clearly recognized by the adjacent skin reaction. The affected skin is hyperaemic, and there may be beads of serum exuded from them. The lesions are of full skin thickness and involve epidermis, dermis and sub-cutis, often with some oedema. They slowly harden and form a (dimple) indentation in the centre. The regional lymph nodes are easily palpable and enlarged to 3-5 times their normal size. Some masses (lumps) may be detected in the subcutaneous

ISSN 2307-8073

tissues and are often distributed throughout the connective tissue and muscle in the body (Diesel 1949). The disease lesions are also developed on the muzzle in the nares and the oropharynx. The muzzle shows a typical ring-like lesion due to sloughing of the necrotic lesions from the healthy surrounding epithelium. Larynx, trachea, alimentary tract particularly the abomasum may also develop lesions (necrosis and ulceration) that lead to develop severe gastro-enteritis. Keratitis is a common complication. Mucopurulent discharges appear from the nares, persistent dribbling from the mouth, coughing and often stertorious and distressed respiration, if the larynx and trachea are involved (Ayre-Smith 1960).

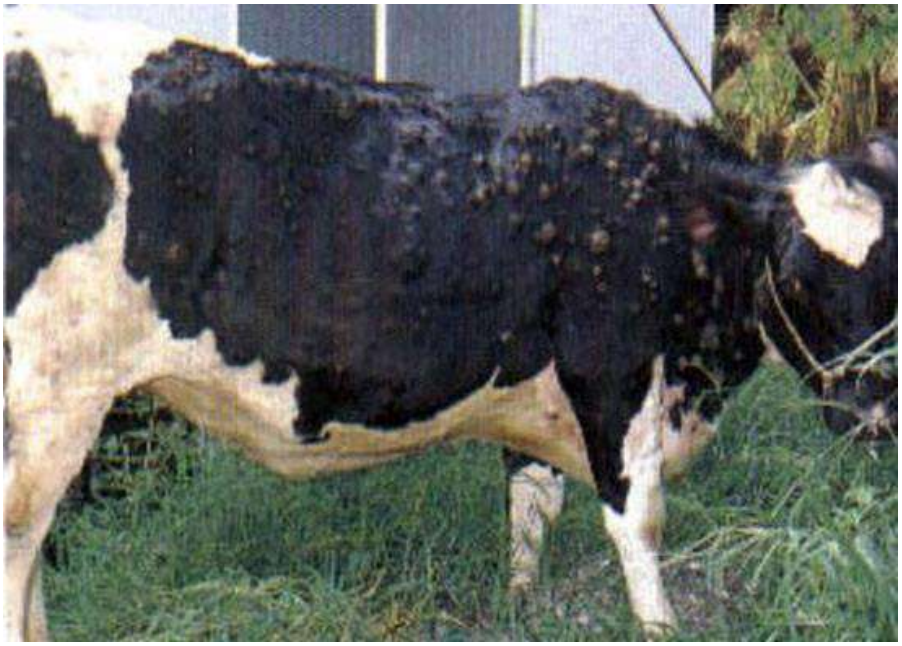
After 2-3 weeks, the skin lesions gradually become harder and necrotic. Several lesions associated with the formation of hard oedematous plaques, cause severe discomfort and pain and inhibit movement. Later on, the "sitfast" of LSD are developed from harder lesions (core of necrotic tissue forms a plug). There is a distinct ring of living tissue around the lesions. Some of "sitfast" may peel off, leaving a full skin thickness hole in the skin, which heals by granulation. Bacteria may invade the hole. The limbs are swelled to several times their normal size due to inflammation, oedema and large areas of necrotic lesions. Hard skin over chronically oedematous limbs may peel off, leaving large areas that can become infected or susceptible to myasis. It was a major concern, when Cochliomyia homnivorax occurred in North Africa. Lesions on the teats may falling away, predisposing animals to mastitis and loss of quarters.

The common sequel of LSD is the pneumonia, associated with a large area of grey consolidation measuring 20-30 mm, which may be fatal. Inhalation of necrotic tissue from lesions higher in the respiratory tract has been approved to be fatal, many months after the initial infection. Abortion is a common sequel of the acute phase of the disease; aborted foetuses and live calves have been observed with skin lesions of LSD. Infertility is a problem following LSD infection; females remain in anoestrous for several months and most infected cow suffering from cessation of ovarian activity mainly due to poor body condition. The infected bulls, which suffer from lesions on the genitalia, may also be infertile for months.

Respiratory, mouth, pharyngeal, and ocular lesions prolong the period of anorexia and recovery. Deterioration in the general condition occurs in the severely affected animals and under range conditions the mortality can be high. The recovered animals suffered from weakness and debility for up to 6 months. The majority of affected animals develop comparatively few nodules and recover uneventfully. LSD is, however, a serious disease affecting production, although the proportion of animals developing chronic complications may be low; less than 5% of those affected (Gezahegn *et al* 2013).

Figure 3. Cow infected with LSD reveals multiple skin nodules (from Iraq recent outbreak)

ISSN 2307-8073



Pathology

1. Gross pathological findings

LSD has well-described gross lesions. Skin nodules are usually uniform in size, firm round and raised, but some may fuse into large irregular and circumscribed plaques. The cut surface of the nodules is reddish-gray, in addition, to the accumulation of the reddish grey serous fluid and edema in the subcutis layer. The resolved lesions appear as indurated which is called "sitfasts" or seclude or may form deep ulcers. The typical circular necrotic alimentary lesions may also be seen on the muzzle, nasal cavity, larynx, trachea, bronchi, inside of lips, gingiva, dental pad, forestomach, abomasum, uterus, vagina, teats, udder and testes (Ali *et al* 1990). Regional lymph nodes are grossly enlarged and can be 3-5 times their usual size, oedematous and having pyaemic foci, in addition to local cellulitis. Muscle tissue and the fascia over limb muscle may be show nodular lesion that are grey-white surrounded by red inflammatory tissue. The same nodules are distributed throughout the carcass. It is about 10-30 mm diameter in the kidney. Interstitial or bronchopneumonia associated with 10-20 mm diameter lesions are also scattered in the lungs. These lesions result from infiltration of the large epithelioid 'celles claveleuses', described by Borrel for sheep pox. The lesions are separated from the necrotic epithelium far from the healthy tissue. The necrotic tissue sloughs away to leave an ulcer that slowly heals by granulation. Severely infected animals may show secondary bacterial pneumonia, tracheal stenosis, acute and chronic orchitis, mastitis with secondary bacterial infection, and similar lesions in the female reproductive tract (Davies *et al* 1971; El-Neweshy *et al* 2012; Kumar 2011).

2. Histopathological findings

Histopathological findings of the LSD disease are very characteristic and provide a basis for diagnosis. The lesions vary considerably depending on the stage of

ISSN 2307-8073

development. In the acute stage of the disease, it is mostly characterised by lesions of vasculitis, thrombosis, infarction, perivascular fibroplasia. Inflammatory cell are infiltrated the infected areas, which includes macrophages, lymphocytes and eosinophils. Keratinocytes, macrophages, endothelial cells and pericytes may be revealed Intracytoplasmic eosinophilic inclusions. The epidermis and dermis layers of the infected animal are showing oedema and infiltrated with large epithelioid macrophage type cells.

There are an oedema and infiltration of the epidermis and dermis with large epithelioid macrophage type cells, which have also been well described for sheep pox. They are found with plasma cells and lymphocytes in early lesions, and in older lesions, fibroblasts and polymorphonuclear leucocytes with some red cells predominate. Endothelial proliferation is seen in the blood vessels of the dermis and subcutis, with lymphocytic cuffing of the blood vessels, which lead to the thrombosis and necrosis. Specific intracytoplasmic inclusions may be found in the various epithelial elements, sebaceous glands and follicular epithelium. These are largely eosinophilic-purple and appear to have a clear halo surrounding them, which is probably a processing artefact. The lesions are substantially the same throughout the body (Burdin 1959; Ali *et al* 1990; El-Neweshy *et al* 2012; Ali and Amina 2013).

Diagnosis

The diagnosis of LSD is based on typical clinical signs combined with laboratory confirmation of the presence of the virus or antigen (Figure 4).

1. A Field presumptive diagnosis of LSD can be based upon the:

A. Morbidity, mortality and clinical signs that reflect LSD such as:

1. Contagious disease with generalised skin nodules
2. A characteristic inverted conical necrosis of skin nodules (sitfast), Enlargement of lymph nodes draining affected areas.
3. Persistent fever, emaciation, and low mortality.
4. Pox lesions of mucous membrane of the mouth, the pharynx, epiglottis, tongue and throughout the digestive tract, mucous membranes of the nasal cavity, trachea and lungs
6. Oedema and areas of focal lobular atelectasis in lungs
7. Pleuritis with enlargement of the mediastinal lymph nodes in severe cases
8. Synovitis and tendosynovitis with fibrin in the synovial fluid
9. Pox lesions may be present in the testicles and urinary bladder

B. Histopathological features

Skin biopsies of early lesions are suitable for histopathology and should be preserved in 10 percent buffered formalin. The most diagnostic histopathological features are:

1. Congestion, haemorrhage, oedema, vasculitis and necrosis are always associated with nodules that are involving all skin layers, subcutaneous tissue, and often adjacent musculature.
2. Lymphoid proliferation, oedema, congestion and haemorrhage.
3. Vasculitis, thrombosis, infarction, perivascular fibroplasia and cellular infiltrates

ISSN 2307-8073

4. Intracytoplasmic eosinophilic inclusions may be seen in different cells.

3. A confirmative diagnosis of LSD can be based upon the:

• **Laboratory investigations and identification of the agent based on** (OIE Terrestrial Manual 2010; OIE 2013):

A. Isolation of the virus

Confirmation of lumpy skin disease in a new area requires virus isolation and identification. Samples for virus isolation should be collected within the first week of the occurrence of clinical signs, before the development of neutralising antibodies (Davies 1991; Davies *et al* 1971).Skin biopsies of early lesions (ones where necrosis has not occurred) provide samples that can be used for virus isolation and electron microscopy. In addition, LSD virus can be isolated from buffy coat from the blood sample collected into EDTA or heparin during the viraemic stage of LSD. Samples should be taken from at least three animals. Samples aspirated from enlarged lymph nodes can be also used for virus isolation. LSD virus grows in tissue culture of bovine, ovine or caprine origin. Bovine dermis cells or lamb testis (LT) cells (Primary or secondary culture), are considered to be the most susceptible cells. LSD capripoxvirus have been also adapted to grow on the chorioallantoic membrane of embryonated chicken eggs and African green monkey kidney (Vero) cells, which is not recommended for primary isolation (OIE Terrestrial Manual 2010).

B. Electron microscopy

Transmission electron microscopic (TEM) diagnosis of LSD can be confirmed within a few hours of receipt of specimens. TEM demonstration of virus in negatively stained preparations of biopsy specimens taken from affected skin or mucous membranes. Mature capripox virions have an average size 320 x 260 nm and are a more oval profile and larger lateral bodies than orthopox virions (OIE Terrestrial Manual 2010).

C. Fluorescent antibody tests

Capripoxvirus antigen can also be identified on the infected cover-slips or tissue culture slides using fluorescent antibody tests.

D. Agar gel immunodiffusion

An agar gel immunodiffusion (AGID) test has been used for detecting the precipitating antigen of capripoxvirus, but has the disadvantage that this antigen is shared by parapoxvirus.

E. Enzyme-linked immunosorbent assay

It is made by using expressed recombinant antigen to produce P32 monospecific polyclonal antiserum and the production of monoclonal antibodies (MAbs) (Carn, *et al* 1994).

ISSN 2307-8073

F. **Polymerase chain reaction (PCR)** and loop-mediated isothermal amplification (LAMP) assay have been used for detection of capripoxviruses with higher sensitivity. (Bowden *et al* 2009; Balinsky *et al* 2008).

- ## Serology

Frozen sera from both acute and convalescent animals are used. Virus neutralisation (cross reacts with all capripoxviruses) and indirect fluorescent antibody test (cross reaction with parapoxviruses) are commonly used. Enzyme-linked immunosorbent assay for the detection of antibodies against capripox virus has been developed using the expressed structural P32 protein (Carn *et al*., 1994; Heine *et al* 1999). Agar gel immunodiffusion tests (This test may give false-positive reactions due to cross reaction with bovine papular stomatitis virus and pseudocowpox virus). Western blot analysis provides a sensitive and specific system for the detection of antibody to capripoxvirus structural proteins, although the test is expensive and difficult to carry out.

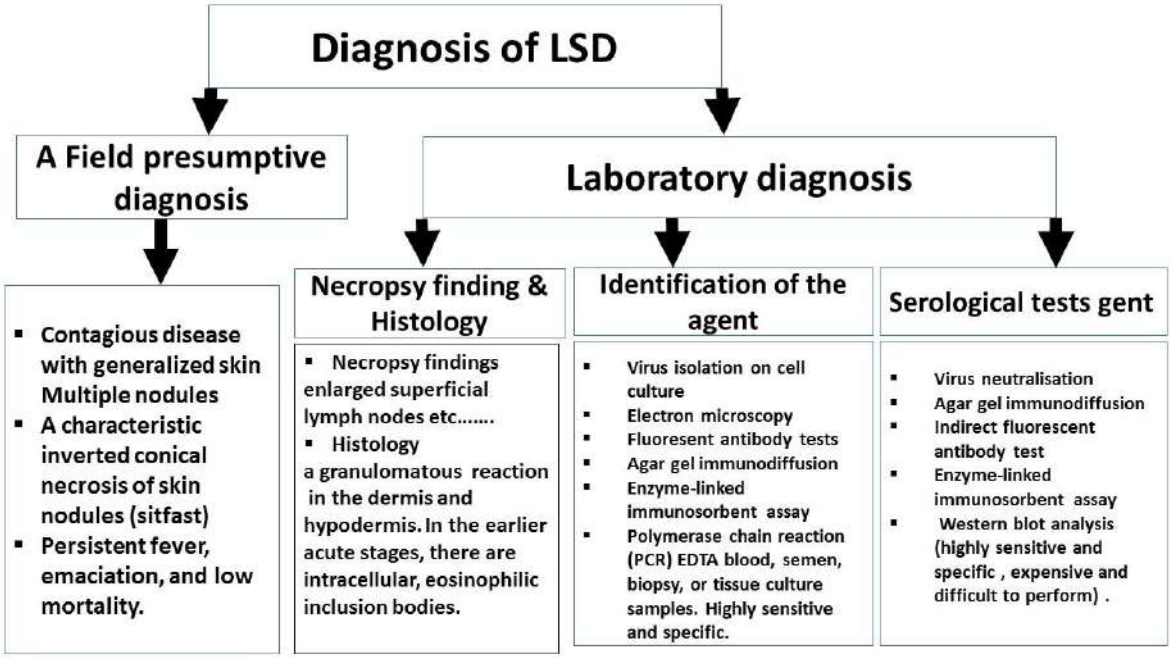
Differential diagnosis

There are many diseases causing similar signs of LSD. It is important to obtain a definite diagnosis to ensure the best preventative and control measures for susceptible herds. LSD can be confused with the following diseases:

- Pseudo-lumpy-skin disease
- Bovine virus diarrhoea/mucosal disease
- Demodicosis (Demodex)
- Bovine malignant catarrhal fever (Snotsiekte)
- Rinderpest
- Besnoitiosis
- Oncocercariasis
- Insect bite allergies

Figure 4. The diagnostic procedures of the LSD

ISSN 2307-8073



Treatment

Lumpy skin disease is caused by virus and, therefore, has no known cure. However, antibiotics, anti-inflammatory drugs or a shot of vitamins are used in some cases to treat secondary bacterial infections or to deal with fever or inflammation and improvement of the animal's appetite.

Control

Control of Lumpy skin disease by quarantine and movement control is not very effective because biting flies and certain tick species are most probably the most important method of transmission of the disease. Although, the control of insects was not effective in preventing the spread of LSD, but use of insecticides together with repellents can be an aid in the prevention of the spread of LSD. LSD outbreaks can be eradicated by quarantines, depopulation of infected and exposed animals, proper disposal of carcases, cleaning and disinfection of the premises and insect control.

LSD control can only be by vaccination or immunoprophylaxis. Live vaccines help control losses from lumpy skin disease in endemic areas. According to OIE, four live attenuated strains of capripoxvirus have been used as vaccines specifically for the control of LSD (Brenner *et al*, 2006; Capstick & Coakley 1961 & 1962; Carn *et al*., 1994). These are: a strain of Kenyan sheep and goat pox virus passaged 18 times in lamb testis (LT) cells or fetal calf muscle cells, Yugoslavian RM 65 sheep pox strain, Romanian sheep pox strain and lumpy skin disease virus strain from South Africa, passaged 60 times in lamb kidney cells and 20 times on the chorioallantoic membrane of embryonated chicken eggs.

The following vaccines have been used in protection of the animal:

ISSN 2307-8073

- Homologous live attenuated virus vaccine (Neethling strain: immunity conferred lasts up to 3 years).
- Heterologous live attenuated virus vaccine (Sheep or goat pox vaccine, but may cause local, sometimes severe reactions). This vaccine is not advised in countries free from sheep and goat pox because the live vaccines could otherwise provide a source of infection for the susceptible sheep and goat populations.
- There is no new generation recombinant capripox vaccines are commercially available.

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Use of antimicrobials in the treatment of calf diarrhea: a systematic review

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Abstract

The objective of this study was to conduct a systematic review of the scientific literature evaluating the efficacy and comparative efficacy of antimicrobials (AMs) for the treatment of diarrhea in calves. Eligible studies were non- and randomized controlled trials evaluating an AM intervention against a positive and negative control, with at least one of the following outcomes: fecal consistency score, fever, dehydration, appetite, attitude, weight gain, and mortality. Four electronic databases were searched. Titles and abstracts (three reviewers) and full texts (two reviewers) were screened. A total of 2899 studies were retrieved; 11 studies met the inclusion criteria. The risk of bias was assessed. Most studies had incomplete reporting of trial design and results. Eight studies compared AMs to a negative control (placebo or no treatment). Among eligible studies, the most common outcomes reported were diarrhea severity ($n = 6$) and mortality ($n = 6$). Eligible studies evaluated very different interventions and outcomes; thus, a meta-analysis was not performed. The risk of bias assessment revealed concerns with reporting of key trial features, including disease and outcome definitions. Insufficient evidence is available in the scientific literature to assess the efficacy of AMs in treating calf diarrhea.

Introduction

Rationale

Gastrointestinal disorders are one of the most prevalent diseases of preweaned dairy calves: approximately 21% of dairy calves in US operations are affected and 76% of them receive antimicrobial (AM) treatment (NAHMS-USDA, 2018; Urie *et al.*, 2018). Similarly, diarrhea is the primary reason for AM treatment in beef calf ranches (Waldner *et al.*, 2013). The primary goal of AM therapy in diarrheic calves is to prevent bacteremia and decrease the number of coliform bacteria in the small intestine (Smith, 2015). However, experts recommended that AM treatments should be limited to scouring calves showing clinical signs of systemic illness (Constable *et al.*, 2008).

In the USA, there is a limited number of AMs with a Food and Drug Administration (FDA) approval for the treatment of gastrointestinal diseases in calves (chlortetracycline, ampicillin, amoxicillin, oxytetracycline, tetracycline, and sulfamethazine; FARAD, 2020). Most of the FDA-approved AM drugs belong to the penicillin or tetracycline class, categorized as critically and highly important AMs for human medicine, respectively (WHO, 2019). Although AMs are widely used for prophylaxis, metaphylaxis, and treatment of infectious diseases in calves (Urie *et al.*, 2018), validated evidence on the efficacy of AMs for the treatment of gastrointestinal disorders in calves is lacking (Smith, 2015).

AM use represents a threat to worldwide public health, as it is one of the main drivers of the emergence of antimicrobial resistance (AMR; Van Boeckel *et al.*, 2015; WHO, 2015; FDA CVM, 2018). Therefore, the judicious use of medically important AM drugs in food-producing animals has been proposed as a key strategy to preserve the effectiveness of currently available AM drugs (WHO, 2015; FDA CVM, 2018; OIE, 2018). Accurate and unbiased evidence on the therapeutic efficacy of AMs to treat infectious diseases is necessary to successfully design evidence-based AM stewardship programs (Sargeant *et al.*, 2019a).

The efficacy of AM treatments should be assessed in multi-arm randomized controlled trials (RCTs), but these are rarely available in the scientific literature. So, research synthesis methods of two-armed RCTs can be used to evaluate AM efficacy (O'Connor *et al.*, 2019). Systematic reviews (SRs) and meta-analyses (MA) are powerful tools that can provide scientifically valid information on the scope and conclusions of the existing literature on AM treatments for calf diarrhea. These synthesis methods are needed to design evidence-based

decision-making guidelines that can be incorporated in AM stewardship programs for livestock.

Objectives

The first objective of this study was to conduct an SR to appraise the scientific literature on the efficacy and comparative efficacy of AM treatments for diarrhea in calves under 6 months of age. The second objective was to conduct an MA to evaluate the efficacy of AM drugs compared to the absence of treatment, alternative non-AM treatments, or other AM drugs used to treat diarrhea in calves under 6 months of age.

Methods

Protocol and registration

An *a priori* review protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P; Moher *et al.*, 2015) and was archived in the University of California eScholarship online repository (https://escholarship.org/uc/item/0nw528h4). In addition, the protocol was published on the Systematic Reviews for Animals and Food (SYREAF) website (http://www.syreaf.org/protocol). Protocol amendments are described below and include screening questions, risk of bias assessment, and summary measures.

Eligibility criteria

Eligibility criteria, search strategy, and screening questions were designed based on the PICOS question format (Population–Intervention–Comparison–Outcome–Study type; EFSA, 2010; O'Connor *et al.*, 2014a). The population of interest was dairy and beef calves under 6 months of age at the time of study enrollment. The intervention of interest was the administration of oral or injectable AMs (antimicrobials; antibiotics and antiprotozoal drugs) after observing clinical signs of diarrhea or after exposing animals to a diarrhea-causing pathogen (challenge studies). Comparisons of interest were the absence of treatment (e.g. placebo, no-treatment), alternative non-AM treatments (e.g. herb extracts, probiotics, lactoferrin, oral rehydration solutions), or other AM treatments (e.g., AM used as positive control). Outcomes of interest were limited to mortality, health [e.g. fecal consistency score (FCS), blood in feces, dehydration (DH), appetite, demeanor, or fever], and performance [e.g. average daily gain (ADG) and feed efficiency]. Only studies assessing the efficacy of AMs to treat animals diagnosed with diarrhea based on clinical signs were relevant. Studies exclusively focusing on pathogen fecal shedding were excluded. The SR was limited to primary research including non-, quasi-, and RCTs with at least one AM and one comparator group. Only peer-reviewed publications were retrieved, and 'gray literature' (literature not formally published, such as theses and dissertations, conference proceedings, trade articles, research reports, and policy documents) was not included (Dickersin *et al.*, 1994). Eligible studies had to be written in English and publicly available, although not necessarily open access. The searching period was based on database coverage, and no limit on publication date was applied.

Search strategy and information sources

The search strategy was designed by an experienced health and veterinary science academic librarian (E. D. F.), with input and reference citation lists from content experts (C. B. C. and N. S. R.). Relevant articles were identified by the principal investigator (C. B. C.) and keywords and indexing terms were mined through Medline (via PubMed, 1966–2020) and CAB Abstracts (via CAB Direct, 1972–2020). After developing the search strategies in CAB Abstracts and PubMed, the search was translated by E. D. F. to Scopus (via Scopus, 1970–2020) and Biosis (via Web of Science, 1926–2020). Keywords from relevant references were gathered and compared to keywords utilized in the previous search. Yale MeSH Analyzer (http://mesh.med.yale.edu/) was also utilized to compare common Medical Subject Headings across articles. Content experts identified keywords or indexing terms based on key pathogens and relevant AMs. During screening, C. B. C. performed a hand-search of relevant manuscripts and reviews using the snowball method and citation searching (https://libguides.library.uu.nl/PiL). The literature search was conducted from 1st to 2nd July 2019, and a search update was made on 29th June 2020. All studies were exported to Mendeley (Mendeley Ltd., Elsevier), where duplicate citations were deleted. The search strategy used for all databases is described in Supplementary material (SM) 1.

Selection process

Covidence SR management software (Veritas Health Innovation, Melbourne, Australia) was used to manage the screening of the title and abstract of all citations retrieved in the search. Three reviewers with veterinary and animal science backgrounds were trained on PICOS format questions prior to screening the title (C. B. C., L. L. S., and M. B. A.), abstract (C. B. C. and L. L. S.), and full text (C. B. C. and L. L. S.). The screening questions included in the protocol were beta-tested with 40 citations, and afterward modified for clarity if needed. For title and abstract screening questions, the possible answers were 'no', 'maybe/unclear', and 'yes'. References moved to the next stage if all title and abstract screening questions were answered 'yes' or 'maybe/unclear'. For full-text screening questions, the possible answers were 'no' and 'yes'. References were included in the SR if all the full-text screening questions were answered 'yes'. References were excluded if all reviewers responded 'no' to one or more questions. Disagreements on manuscript inclusion were resolved by consensus and if necessary, an additional researcher (N. S. R.) was consulted. The final screening questions utilized were:

Title screening

(1) Does the title indicate cattle as the subject of study?
(2) Does the title describe the use of an AM treatment?

Abstract screening

(1) Does the abstract describe a controlled trial?
(2) Does the abstract describe a study of diarrhea in calves?
(3) Does the abstract describe one or more intervention groups of an AM treatment regimen?
(4) Does the abstract report at least one outcome related to clinical cure or performance?

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Full-text screening

In this final screening level, the previous six questions and the following questions were used:

(1) Is the enrollment age of subject cattle ≤6 months?
(2) Are AM given after the diagnosis of diarrhea or the onset of clinical signs?
(3) Does the study evaluate clinical outcomes of AM treatment?

Studies evaluating the efficacy of AM use in control (metaphylaxis) and prevention (prophylaxis) of disease, as defined by the American Veterinary Medical Association (AVMA, 2020), were excluded. Studies where AM treatments were given as growth promoters, and studies with unclear or no reporting primary data were not considered. The reasons for manuscript exclusion were recorded at this level.

Data collection process

The data extraction process was completed following the guidelines by Sargeant and O'Connor (2014). Two reviewers (C. B. C. and L. L. S.) independently used pre-designed spreadsheets to collect data (Excel 2010, Microsoft Corp., Redmond, WA). Data extraction disagreements were resolved by discussion until a consensus was reached; if needed, a third reviewer (N. S. R.) was consulted. Study-level data included population, interventions, comparators, and outcomes for each independent study. Population data included: breed, sex, enrollment age, housing, inclusion criteria, and sample size. Intervention and comparator-level data were extracted and included: randomization process, group size, treatment features (active ingredient, dose, route, length, and frequency), complementary treatments (e.g. fluid therapy and anti-inflammatory drugs), and features of personnel who delivered treatments (e.g. training or blindness). Additionally, pathogens (e.g. genus and species) and infection type (e.g. challenge study or natural infection) were extracted. Outcome data extracted included: type, evaluation features (e.g. assessment methods, evaluation period, and frequency of measurements), and features of personnel who assessed clinical outcomes (e.g. training or blindness). Treatment failure and success definitions, when these were available, were extracted – without modifications – from the original manuscripts. The summary effects of the outcomes were extracted from either adjusted (if available) or unadjusted data as well as their corresponding measures of variability. Moreover, the significance and variability of the reported outcome were recorded when available [e.g. standard deviation, standard error, odds ratio, relative risk, confidence intervals (CIs), and *P*-value].

Risk of bias assessment

The risk of bias at the outcome level was independently assessed by three reviewers (C. B. C., R. B. L., and L. L. S.) using the Cochrane Risk of Bias Tool for Randomized Trials (Sterne *et al.*, 2019). Five commonly used domains (bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of reported results) and a novel domain (bias related to disease definition; SM 2) were assessed. As described below, signaling questions were modified following the approach described by Sargeant *et al.* (2019a, 2019b) in prior livestock synthesis studies. In the randomization process domain, the question 'was the allocation sequence random?' was modified to 'was the study randomized?'. The answers to this question were modified to 'probably no' if the study did not report data on sequence generation, 'probably yes' if the study reported random sequence allocation but not the randomization process, and 'yes' when the study reported a random component in the sequence generation process (e.g. computer random number generator). Also, the allocation sequence concealment question was not included as it is unlikely that a farmworker, producer, or researcher would have a treatment preference for any given calf. In the domain regarding deviations from intended interventions, the question 'were participants aware of their assigned intervention during the trial?' was always answered as 'no', as the 'participants' in all studies were calves. This domain also inquires about the blinding of study personnel; for the purposes of this SR, the animal caregivers and/or people responsible for delivering treatment were the relevant study personnel. The risk of bias tool was tested with three studies to ensure consistency across reviewers (Sargeant and O'Connor, 2014). Reviewers were trained on the risk of bias tool, and disagreements between reviewers were resolved by consensus to adjudicate the final judgment. The outcome chosen for bias assessment was the severity of FCS or diarrhea, but if not reported, diarrhea duration was used instead.

Synthesis of results

As described in the study protocol, the goal of this SR was to conduct an MA to evaluate the efficacy of AMs in the treatment of calf diarrhea. Our SR identified few eligible manuscripts; there was wide variability in interventions and outcomes across studies. Scarcity of the scientific literature and heterogeneity among studies made it unfeasible to address the review question. Thus, no quantitative synthesis could be performed, and heterogeneity was not formally assessed. Following the PRISMA guidelines, study results were summarized in forest plots for visualization purposes.

Summary measures

The effect size [risk ratio (RR) or mean difference] was calculated for the most common outcomes reported at the group level: diarrhea (or fecal score) severity and calf mortality. For categorical data, mean difference and 95% CIs were calculated using the OpenEpi online tool (https://www.openepi.com/Mean/t_testMean.htm); pooled standard error reported in each original manuscript was used in these calculations. For binary data, the RR and 95% CI were calculated using MedCalc Statistical Software version 20.0.5 (MedCalc Software, Ostend, Belgium). For RR calculation, calves that received the intervention were considered exposed, and calves that were given the comparator were considered unexposed. For FCS or diarrhea, RR was calculated using mild to severe diarrhea cases in exposed and unexposed calves. Post-hoc analysis was not necessary when manuscripts reported the effect size as RR.

Results

Study characteristics

Results below correspond to SR results only, as an MA could not be conducted due to scarcity of studies and differences in interventions and outcomes among selected studies. The search retrieved 2899 publications from which 102 full-text manuscripts were assessed for eligibility (Fig. 1). In total, 11 manuscripts

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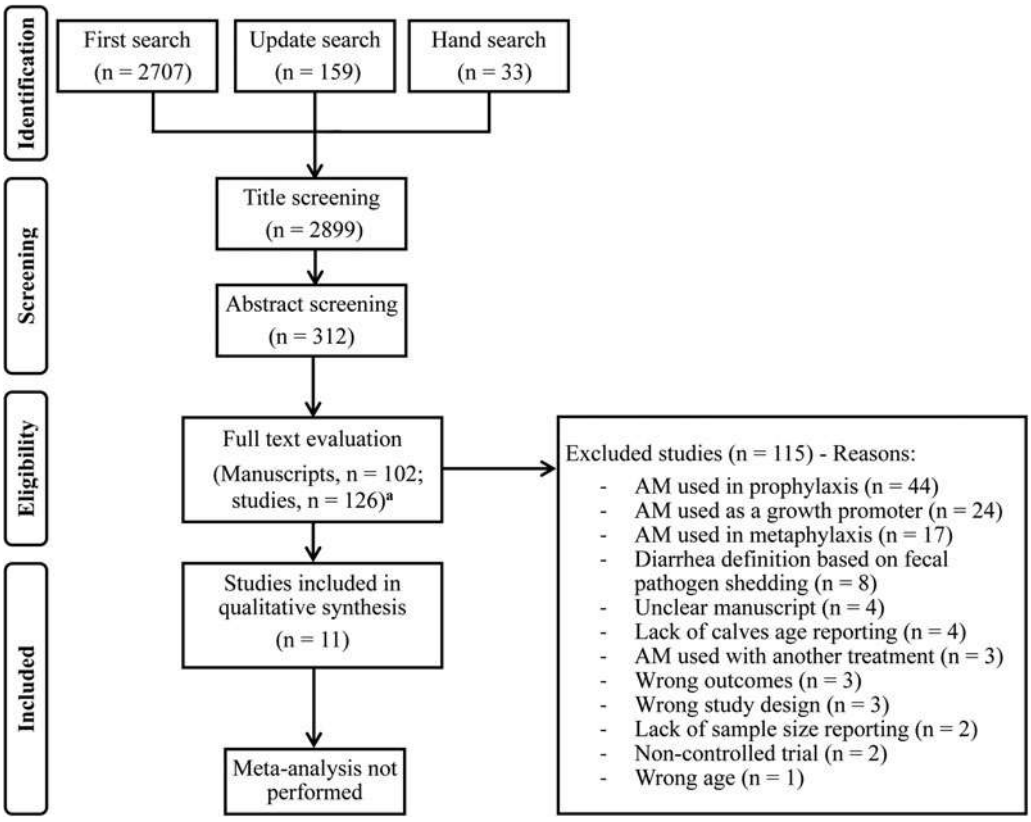

Fig. 1. Flow diagram illustrating the selection of eligible studies for the systematic review of the efficacy of antimicrobials in the treatment of calf diarrhea (Adapted from the PRISMA guidelines). [a]102 full-text manuscripts which contained 126 independent studies.

Table 1. Characteristics of eligible trials investigating the efficacy of AMs in the treatment of calf diarrhea

Study	Country	Housing (farms)	*n*	Age[a]	Breed type	Main etiological agent
Challenge						
Bywater (1977)	England	NR	42	5–10 days	NR	*E. coli*
Fecteau *et al.* (2003)	The United States	University/research	29	At birth	Dairy	*Salmonella typhimurium*
Lofstedt *et al.* (1996)	Canada	University/research	30	≤6 h	Dairy	*E. coli*
Ollivett *et al.* (2009)	The United States	University/research	23	At birth	Dairy	*Cryptosporidium parvum*
Schnyder *et al.* (2009)	Switzerland	University/research	6	1–3 days	NR	*C. parvum*
Silva *et al.* (2010)	Brazil	NR	12	10–15 days	NR	*Salmonella Dublin*
White *et al.* (1998)	England	NR	38	1–2 w	NR	*E. coli*
Natural infection						
Grandemange *et al.* (2002)	France and Belgium	Commercial	184	≤5 days	Beef	*E. coli*
Grimshaw *et al.* (1987)	England, France, and Germany	University/research	452	3–10 days	Dairy	*E. coli*
Sheldon (1997)	United Kingdom	Commercial	65	1–30 days	Dairy	*E. coli*
Sunderland *et al.* (2003)	France and Germany	Commercial	402	7–90 days	Both	*E. coli*

NR, not reported.
[a]Age at enrollment.

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containing 11 unique studies met all the inclusion criteria and were included in the SR. The main characteristics of the 11 selected studies are described in Table 1. Four studies reported the funding source [private (Lofstedt *et al.*, 1996; Fecteau *et al.*, 2003), public (Silva *et al.*, 2010), or mixed (Ollivett *et al.*, 2009)] whereas seven did not. No study provided a sample-size calculation, and randomization was unclear in one study (Bywater, 1977).

Intervention and comparator features

Intervention (treatment) and comparator (control) groups are described in Table 2. No study provided information about the training of personnel administering treatments, and only two studies reported blinding of personnel (Sheldon, 1977; Ollivett *et al.*, 2009). Due to irrelevant interventions, one or more groups (arms) were not considered: (1) unchallenged calves treated or non-treated (Fecteau *et al.*, 2003; Schnyder *et al.*, 2009; Silva *et al.*, 2010); (2) AMs in combination with other treatments (Bywater, 1977; Silva *et al.*, 2010); and (3) AMs given as prophylactic intervention (Schnyder *et al.*, 2009).

Outcomes and definitions

Clinical outcomes

The most common clinical outcomes evaluated (FCS, temperature, DH, appetite, and attitude) are described in Table 3. Other clinical variables evaluated included eye position (Lofstedt *et al.*, 1996) and blood in feces, tenesmus, and sucking reflex (Grandemange *et al.*, 2002). In three studies, outcome assessors were reported to be blinded and identified as veterinarians (Sunderland *et al.*, 2003), vet students (Ollivett *et al.*, 2009), or researchers (White *et al.*, 1998); but eight studies did not provide this information.

Performance outcomes

One study assessed ADG (Ollivett *et al.*, 2009). Bodyweight gain was evaluated in 6 studies (Bywater, 1977; Grimshaw *et al.*, 1987; White *et al.*, 1998; Fecteau *et al.*, 2003; Schnyder *et al.*, 2009; Silva *et al.*, 2010), however, one study did not report results (Schnyder *et al.*, 2009). Only one manuscript reported the tool or method used to weigh calves (digital scale; Ollivett *et al.*, 2009).

Health definitions

Five studies reported a definition of diarrhea (Bywater, 1977; Grimshaw *et al.*, 1987; Grandemange *et al.*, 2002; Sunderland *et al.*, 2003; Ollivett *et al.*, 2009); it was exclusively based on FCS but its description and score-point system highly varied across studies. Five studies used the term 'diarrhea' but provided no definition (Lofstedt *et al.*, 1996; White *et al.*, 1998; Fecteau *et al.*, 2003; Schnyder *et al.*, 2009; Silva *et al.*, 2010), and one study defined health events based on abnormal FCS without using the term 'diarrhea' (Sheldon, 1997). Two studies reported treatment failure and success (Sheldon, 1997; Grandemange *et al.*, 2002), but the term 'failure' was not defined in Sheldon (1997).

Results of specific outcomes

Mortality

Calf mortality was reported in six studies; the calculated RR for each study was represented as a forest plot (Fig. 2). The RR for three of the comparisons (Amoxicillin vs No treatment; Sulbactam: Ampicillin vs Placebo; Ampicillin vs. Placebo) favored intervention relative to control (the CI did not include 1).

Severity of diarrhea

Seven studies reported the severity of diarrhea (Lofstedt *et al.*, 1996; Sheldon, 1997; White *et al.*, 1998; Grandemange *et al.*, 2002; Sunderland *et al.*, 2003; Ollivett *et al.*, 2009; Silva *et al.*, 2010). However, one study (Grandemange *et al.*, 2002) was not considered due to incomplete reporting. Diarrhea severity was reported as RR in one manuscript (Olivett *et al.*, 2009) and calculated in five manuscripts [mean difference ($n = 2$); RR ($n = 3$); Fig. 3]. No comparison favored intervention relative to the comparator.

Additional results

A summary of all the statistically significant treatment effects reported in each of the 11 studies is provided in SM 3. Three studies reported assessment of adverse effects after the intervention; two studies found an absence of adverse effects (Lofstedt *et al.*, 1996; Sunderland *et al.*, 2003); and one study observed an increase in diarrhea severity after AM treatment (Schnyder *et al.*, 2009). One study informed of relapse in clinical signs after completing the AM and positive control interventions (Grandemange *et al.*, 2002).

Risk of bias assessment

The risk of bias at the outcome level was based on the severity of diarrhea (or FCS; Lofstedt *et al.*, 1996; Sheldon, 1997; White *et al.*, 1998; Grandemange *et al.*, 2002; Sunderland *et al.*, 2003; Ollivett *et al.*, 2009; Silva *et al.*, 2010) or diarrhea duration (Bywater, 1977; Grimshaw *et al.*, 1987; Fecteau *et al.*, 2003; Schnyder *et al.*, 2009). Results of the risk of bias assessment for each domain are shown at the study level (Fig. 4) and as the proportion across all included studies (Fig. 5).

Discussion

Dairy and beef calves are often affected with gastrointestinal disorders and treated with AMs (Waldner *et al.*, 2013; NAHMS-USDA, 2018); however, it is unclear if AMs are effective for the treatment of calf gastrointestinal disorders (Smith, 2015). The present work aimed to support the development of calf AM use guidelines by appraising the scientific literature on the efficacy and comparative efficacy of different AM treatments for diarrhea in calves under 6 months of age. Although diarrhea in calves is most common during the first 2 months of life (Preweaning period), we chose an inclusive age criterion because weaning time and age at diarrhea events may vary with management (e.g. production system, breed, and country). Our SR identified 11 relevant studies; nevertheless, the limited number of studies and the differences in interventions (AM class and type of pathogenic agent) prevented us from pursuing a MA evaluation (Valentine *et al.*, 2010). Overall, the eligible studies indicated that diarrhea severity ($n = 4$, challenge) and mortality ($n = 3$, challenge; $n = 3$, natural infection) were numerically inferior after AM intervention; but only three of the aforementioned studies showed significant statistical differences for diarrhea severity ($n = 1$) and mortality [challenge ($n = 1$) and natural infection ($n = 1$)].

Prior SRs evaluating the efficacy of AMs in livestock were also unable to complete a MA due to the heterogeneity of the

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Table 2. Intervention and comparator groups from studies included in the SR of the efficacy of AMs in the treatment of calf diarrhea

	Intervention					Comparator				
Study	Active ingredient	Dose[a]	Route	Length[b]	Frequency[c]	Active ingredient	Dose[a]	Route	Length[b]	Frequency[c]
Challenge										
Bywater (1977)	Amoxicillin	400 mg TD	PO	2 days	q12h	No treatment	–	–	–	–
						Oral rehydration solution	2000 ml TD	PO	2 days	q12h
Fecteau *et al.* (2003)	Ceftiofur	5 mg kg^{-1}	IM	5 days	q24h	No treatment	–	–	–	–
Lofstedt *et al.* (1996)	Sulbactam:ampicillin	3.3:6.6 mg kg^{-1}	IM	3–7 days	q24h	Placebo	3 ml TD	IM	3–7 days	q24h
	Ampicillin	6 mg kg^{-1}	IM	3–7 days	q24h					
Ollivett *et al.* (2009)	Nitazoxanide	1504 mg TD	PO	5 days	q12h	Placebo	–	PO	5 days	q12h
Schnyder *et al.* (2009)	Nitazoxanide	15 mg kg^{-1}	PO	10 days	q12h	No treatment	–	–	–	–
Silva *et al.* (2010)	Florfenicol	20 mg kg^{-1}	IM	0–2 days	q48h	No treatment	–	–	–	–
White *et al.* (1998)	Danofloxacin	1.25 mg kg^{-1}	IM	3 days	q24h	Placebo	1 ml/20 kg	IM	3 days	q24h
						Baquiloprim:sulfadimidine	10 mg kg^{-1}	IM	3 days	q24h
Natural infection										
Grandemange *et al.* (2002)	Marbofloxacin	1 mg kg^{-1}	PO	3–7 days	q24h	Amoxicillin:clavulanic acid	12.5 mg kg^{-1}	PO	3 days	q12h
Grimshaw *et al.* (1987)	Sulbactam:ampicillin	3.3:6.6 mg kg^{-1}	IM	3–7 days	q24h	No treatment	–	–	–	–
	Ampicillin	6.6 mg kg^{-1}	IM	3–7 days	q24h					
Sheldon (1997)	Florfenicol	20 mg kg^{-1}	IM	0–2 days	q48h	Baquiloprim:sulfadimidine	20 mg kg^{-1}	IM	2 days	q48h
Sunderland *et al.* (2003)	Danofloxacin	6 mg kg^{-1}	SC	0–2 days	q48h	Gentamicin	4 mg kg^{-1}	IM	3 days	q12h
						Baquiloprim:sulfadimidine	40 mg kg^{-1}	PO	0–2 days	q48h

PO, oral; IM, intramuscular; SC, subcutaneous; q24h: every 24 h; q12h: every 12 h; q48h: every 48 h.
[a]Doses are reported as mg kg^{-1} (milligrams per kilogram of body weight) or as mg or ml TD (total dose in milligrams or milliliters).
[b]Ranges in the treatment length are related to time to cure.
[c]Frequencies are indicative of the frequency reported by the original manuscript; these could briefly differ from the original value.

Table 3. Scoring systems for clinical outcomes evaluated by studies included in the SR of the efficacy of AMs in the treatment of calf diarrhea

Study	Evaluation period (days)[a]	Fecal consistency	Attitude	DH (criteria)	Appetite	Fever
Challenge						
Bywater (1977)	0 to 10	0–3[b]	0–2[b]	0–2[b]	NR	NR
Fecteau *et al.* (2003)	−4 to 13	0–1[b]	0–4	–	0–3	>39.2°C
Lofstedt *et al.* (1996)	0 to 7	0–4	0–4	0–3 (skin)	–	>40°C
Ollivett *et al.* (2009)	−5 to 10	1–3[c]	1–4[b]	–	–	NR
Schnyder *et al.* (2009)	−1 to 28	Solid–liquid[c]	–	–	–	–
Silva *et al.* (2010)	−2 to 5	0–2[b]	–	–	–	NR
White *et al.* (1998)	0 to 6	0–3[b]	0–3	Absent–severe[b]	NR	–
Natural infection						
Grimshaw *et al.* (1987)	0 to 7	0–3	–	–	–	–
Grandemange *et al.* (2002)	0 to 3, 7	1–5	1–4	1–4 (skin)	1–2[b]	>39.5°C
Sheldon (1997)	0, 2, 4, 10	0–3[b]	0–4[b]	NR	–	≥39.5°C
Sunderland *et al.* (2003)	0 to 11	Absent–severe diarrhea	Absent–severe depression	Absent–severe (skin)	–	–

NR, outcome with assessment methods not reported.
[a]Relative to treatment onset; evaluation days are indicative of the period reported by the original manuscript, so these could differ from the original value.
[b]Not clearly described.
[c]Reference provided for the scoring system method.

interventions across primary studies (O'Connor *et al.*, 2006; Sargeant *et al.*, 2019a; 2019b). Even though very few studies were identified in our SR, it is plausible that additional valid research data exist but have not yet been published in peer-review publications, especially if data were generated to support drug label claims or if the study results refuted the initial hypothesis (Constable, 2004; Wellman and O'Connor, 2007). It should be noted that a large number of studies were excluded because they evaluated the efficacy of AMs following a prophylaxis or metaphylaxis treatment approach, or because they defined 'diarrhea' based on fecal pathogen shedding instead of clinical signs.

In livestock clinical trials, the accuracy of the outcome measured has raised concerns due to incomplete reporting of methods and study design (Burns and O'Connor, 2008; Sargeant *et al.*, 2009; Winder *et al.*, 2019). However, in the future, the standards of quality clinical trials may improve, as some relevant journals are now requesting authors to use the REFLECT statement (O'Connor *et al.*, 2010), a guide for standardized design and reporting, prior to considering a manuscript for publication. In our SR, most studies were designed as challenge experiments. However, there are limitations associated with challenge studies, as they tend to result in exaggerated treatment effects and do not provide a high level of evidence for the effectiveness of an intervention in a commercial setting (Sargeant *et al.*, 2009, 2019a).

Based on the current FDA indications, most studies included in the SR used AM outside label claims. Marbofloxacin (broad-spectrum fluoroquinolone for dogs and cats) and nitazoxanide (human cryptosporidiosis) are not labeled in the USA for use in cattle or calves, and ceftiofur, danofloxacin, and florfenicol are labeled for calf treatments but for ailments other than diarrhea. Ampicillin and amoxicillin were the only treatments with FDA approval for the treatment of *Escherichia coli* enteritis in calves. However, the treatment length of ampicillin in these studies was outside label recommendations. The extra-label use of fluoroquinolones (e.g. danofloxacin and marbofloxacin) and cephalosporins (e.g. ceftiofur) is totally prohibited in food animals due to the high risk of AMR emergence based on the 'Animal Medicinal Drug Use Clarification Act of 1994' and '21 Code Federal Regulations 530' (FDA, 2021). Also, the route of administration differed across studies, orally (amoxicillin, marbofloxacin, and nitazoxanide) or injectable drugs (ampicillin, sulbactam:ampicillin, ceftiofur, florfenicol, and danofloxacin). Differences in route of administration may have also contributed to differences in treatment response; oral administration of AMs may induce changes in the microbiome and aggravate diarrhea presentation (Smith, 2015).

Furthermore, our SR revealed that few relevant studies included, as an intervention, the most common AM chosen to treat calf diarrhea in California commercial operations (sulfonamides as the first choice; ceftiofur products as the second choice; Okello *et al.*, 2021). Although the knowledge that SR provides about AM efficacy and effectiveness is important, it is clearly not the only metric of importance in AM selection. The work of veterinarians and practitioners is key to improving AM use in livestock; other relevant factors that guide veterinarians in AM treatment selection are treatment algorithms and protocols, AM stewardship guidelines, local AM prescribing policies, label recommendations, sensitivity testing results for target animals, and cost–benefit analysis (O'Connor *et al.*, 2019).

Consistent with previous SR in livestock, issues with the risk of bias assessment were observed related to incomplete reporting of the randomization process and the blindness of personnel who delivered treatments and outcome assessors (Francoz *et al.*, 2017; Sargeant *et al.*, 2019b). Randomization was classified as a high-risk grade based on unclear allocation to the treatment as the randomization process was not described, or randomization

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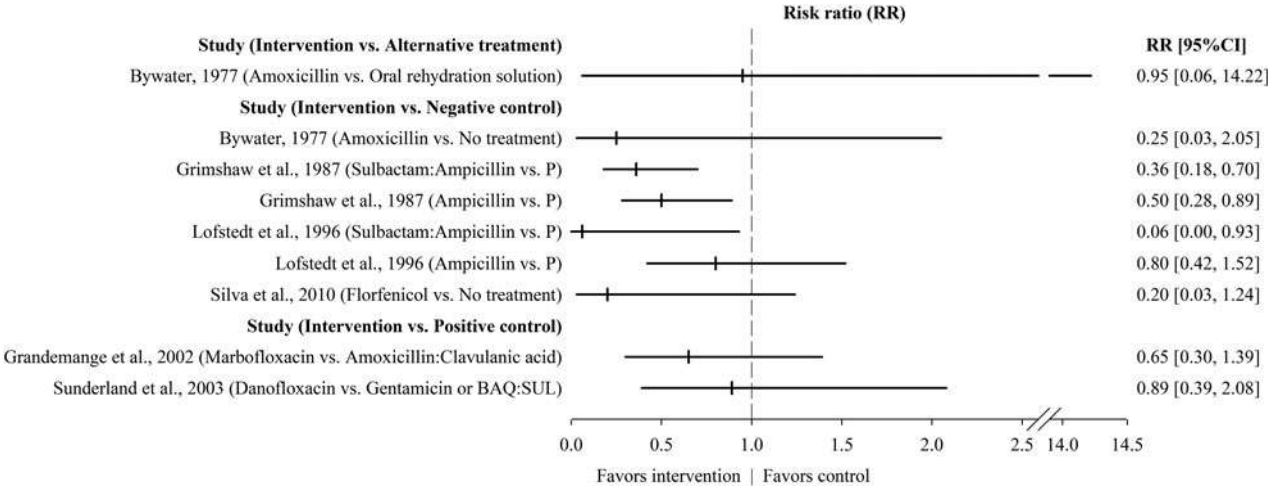

Fig. 2. Forest plot to illustrate the results about mortality from the studies included in the systematic review of the efficacy of antimicrobials in the treatment of calf diarrhea. **P** = Placebo; **BAQ:SUL** = Baquiloprim:Sulphamidine; **CI** = Confidence intervals.

was not mentioned. The most frequent reason for a high-risk classification for blinding of both personnel who delivered treatments and outcome assessors was the absence of blinding reporting. The lack of blinding of personnel delivering treatments could influence the care for the calves during the study. Similarly, outcome assessment could be influenced by knowledge of the intervention delivered, especially for subjective outcomes, such as FCS and DH (Francoz *et al.*, 2017; Sterne *et al.*, 2019). All relevant manuscripts except one were linked to a pharmaceutical company, and that could potentially introduce a source of bias. Furthermore, none of the studies included in our SR sample size calculation, which is consistent with previous reviews (Haimerl *et al.*, 2012; Winder *et al.*, 2019). This might have introduced a publication bias, as underpowered studies with non-significant results are less likely to reach peer-review journals (Sargeant *et al.*, 2009, 2019a). The risk of bias tool was modified to introduce a new domain related to the definition of disease. Most studies were classified with a high risk of bias based on this domain, as the diarrhea definition was missing in about half of the studies, and when reported, the definition was only based on a single outcome. This could lead to biased results due to unnecessary AM administration to diarrheic calves without signs of systemic illness (Constable *et al.*, 2008). Our results are consistent with other SRs which highlighted the lack of disease definition in clinical trials in cattle (Naqvi *et al.*, 2018). Similarly, treatment success and failure definitions were rarely reported; thus, it was difficult to accurately evaluate study results, assessment methods of treatment efficacy, and likely variation sources related to health definitions (Kelly and Janzen, 1986; Wellman and O'Connor, 2007).

In the relevant manuscripts, the evaluation of clinical signs of health disorders was subjective and very diverse across studies. Although FCS was evaluated in all studies, the scoring systems varied highly, even when FCS had the same numerical scale. Additionally, many studies provided a vague description of the FCS categories with only two studies stating a reference; however, those references for FCS methods reported non-validated, unreferenced, and incomplete FCS evaluation methods. No other fecal features beyond consistency were evaluated, and diarrhea

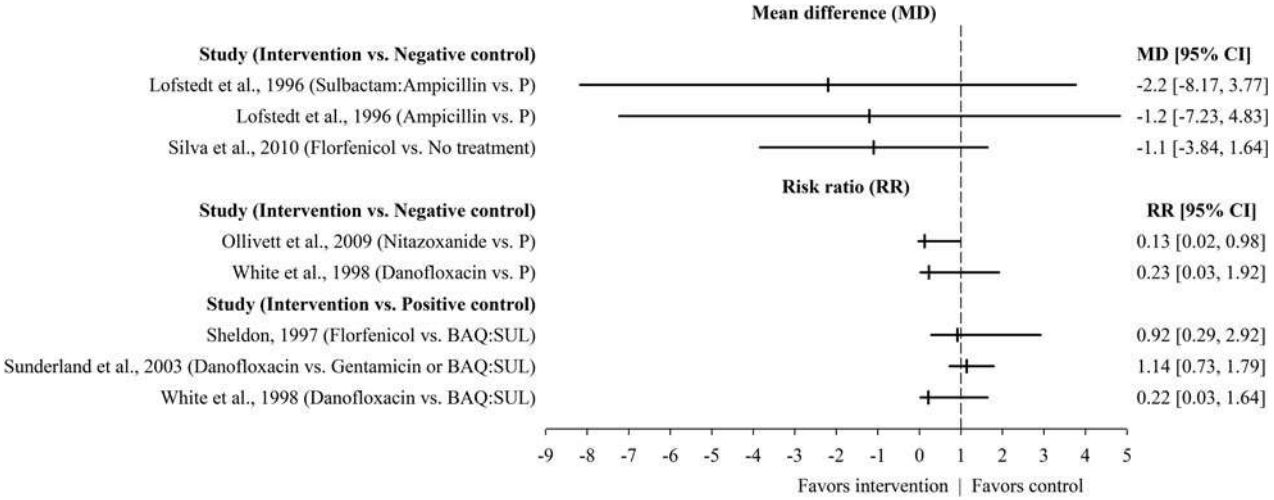

Fig. 3. Forest plot to illustrate the effects of AMs on the severity of FCS or diarrhea from the studies included in the SR of the efficacy of AMs to treat calf diarrhea. P, placebo; BAQ:SUL, baquiloprim:sulfadimidine; CI, confidence intervals.

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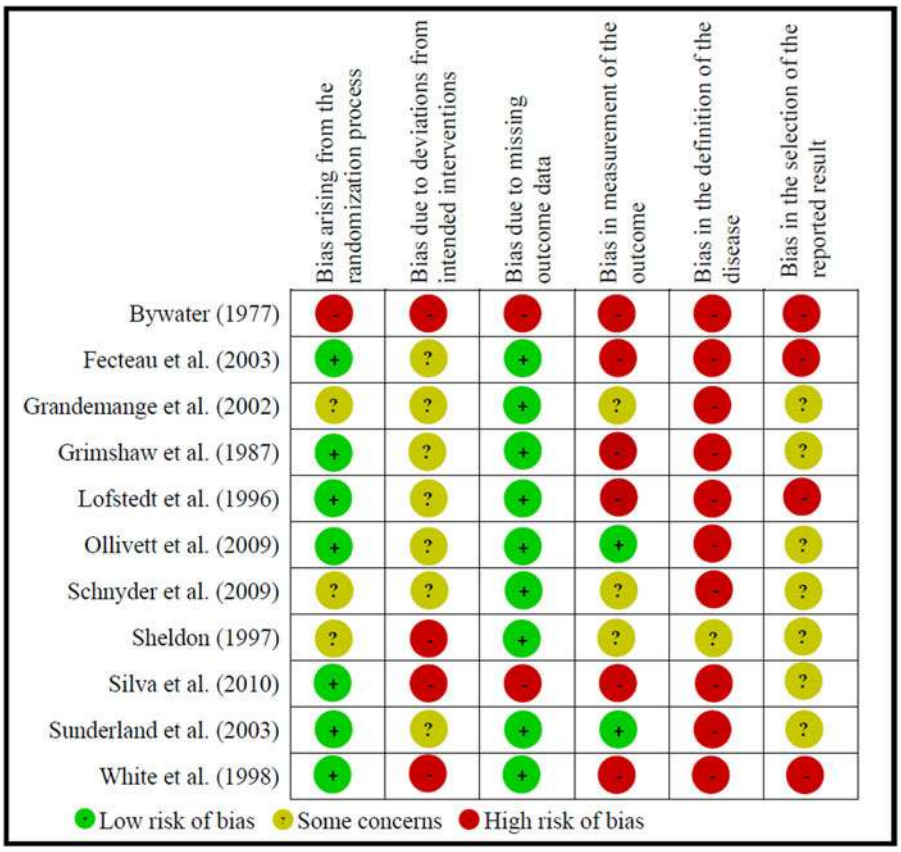

Fig. 4. Risk of bias summary: review authors' judgments about each risk of bias domain for each of the 11 studies included in the SR on the efficacy of AMs in the treatment of calf diarrhea.

severity classification was provided in a single study. Some of the secondary clinical signs evaluated included DH, fever, anorexia, and depression, but their evaluation methods varied across studies, lacked references, and were subjective. DH was evaluated based on skin elasticity without considering body fat, skin location, animal position, and age (Constable *et al.*, 1998). Four studies evaluated fever, but the difference between the maximum and minimum threshold for fever definition reached nearly 1°C across studies, and none of the studies accounted for possible inaccuracies in body temperature assessment related to physiological, environmental, and procedure methods (Hill *et al.*, 2016). Similarly, scoring systems for attitude and appetite were based on empirical and subjective measurements, and highly differed across studies. Overall, the lack of standardized evaluation methods across the 11 relevant studies was concerning, as low reliability in both the measurement of outcomes and health definitions could contribute to decreased statistical power and thereby an under- or over-estimation of treatment effects (Sargeant *et al.*, 2009). Over four decades ago, calf health evaluation guidelines were proposed to make reporting more uniform across research studies (Larson *et al.*, 1977); however, these guidelines have not been adopted, most likely because of their level of complexity (Kertz and Chester-Jones, 2004). Current industry guidelines for calf diarrhea suggest limiting AM treatments to calves with loose stools that also show systemic signs of illness (e.g. inappetence, DH, lethargy, pyrexia), blood or mucosal shreds in their stool, or concurrent infections (Constable *et al.*, 2008; McGuirk, 2008). None of the relevant studies attained this definition; challenge studies treated all exposed animals, and in natural infection studies, treatment was merely based on FCS. Future studies should address this lack of standardized, validated calf health definitions, which results in heterogeneous treatment decisions and cure definitions. The incorporation and combination of validated health assessment methods are key to accurately identifying sick calves, increasing treatment success, and improving animal welfare both inside and outside of research (McGuirk, 2008; Cramer *et al.*, 2016). Furthermore, standardized assessment methods would lead to greater uniformity in study designs (Larson *et al.*, 1977), making the interpretation and comparison of livestock experiments easier. Moreover, objective outcomes, such as ADG, mortality, and laboratory outcomes, could increase the reliability of studies and the ability to summarize the effect size of interventions. However, in our SR, only one study assessed ADG, six studies reported mortality, and the reported laboratory outcomes were highly diverse and limited to a single evaluation.

Finally, this SR had several strengths; it followed a protocol that was reported in accordance with PRISMA-P (Moher *et al.*, 2015); it adhered to the guidelines for SR in animal agriculture and veterinary medicine (O'Connor *et al.*, 2014a, 2014b; Sargeant and O'Connor, 2014); the search strategy, which used multiple electronic databases, was designed with support from a librarian in order to identify the highest number of available studies; and to increase the reliability of the process, the screening, data extraction, and the risk of bias assessment were independently performed by two or more reviewers with a background in veterinary and animal science as well as in research synthesis methods (Sargeant and O'Connor, 2014).

On the other hand, our SR could have some limitations. We did not consider gray literature as a relevant source. On average, only 50% of abstracts reporting the results of RCTs reach full publication, and the calculated abstract-to-publication ratio for some bovine conferences is <10% (Dickersin *et al.*, 1994; Brace *et al.*,

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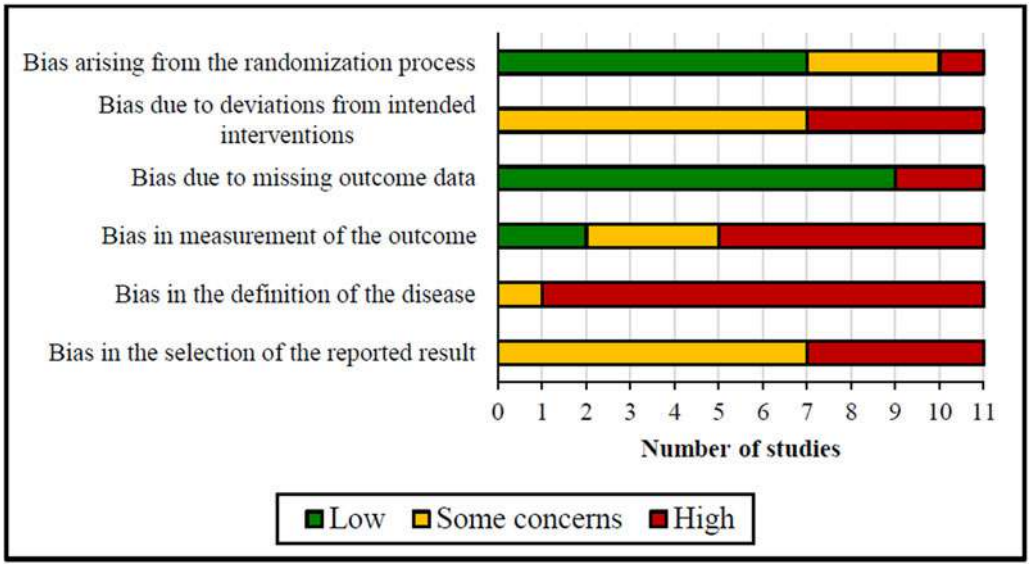

Fig. 5. Risk of bias graph: review authors' judgments about each risk of bias domain presented as percentage across all included studies ($n = 11$) in the SR of the efficacy of AMs in the treatment of calf diarrhea.

2010). Thus, excluding these studies could result in lower precision in the estimate of intervention effect and may result in biased results by introducing publication bias (Dickersin *et al.*, 1994; Sargeant and O'Connor, 2014). However, excluding gray literature may have had a limited impact, as it usually involves short abstracts with not enough data to conduct research synthesis methods (Burns and O'Connor, 2008; Brace *et al.*, 2010; Sargeant and O'Connor, 2014). Another source of bias may be the exclusion of potentially relevant articles published in a language other than English. In veterinary medicine, the impact of language restrictions remains unknown (Burns and O'Connor, 2008), while in human medicine, limiting the language of publication of trial reports to English in SR of conventional interventions (e.g. AMs) does not change the estimates of the effectiveness of an intervention (Moher *et al.*, 2003; Pham *et al.*, 2005). Therefore, the impact of exclusion of manuscripts in languages other than English was likely minimal in the present SR.

Conclusions

At present, the efficacy of AMs in the treatment of calf diarrhea cannot be evaluated using MA methods, as the SR identified few relevant studies testing heterogeneous interventions. Our SR revealed important limitations in study design and reporting, which future studies should overcome in order to perform a valuable MA evaluation of the efficacy of AMs in the treatment of calf diarrhea. The interventions tested should reflect common on-farm treatment approaches, the research community needs to reach an agreement on the definition and outcome evaluation systems of diarrheal disease, and studies should adhere to reporting guidelines.

Supplementary material. The supplementary material for this article can be found at https://escholarship.org/uc/item/0nw528h4#supplemental.

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Conflict of interest. No author has conflicts to declare.

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