

The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of Rift Valley Fever in Animals

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The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of Rift Valley Fever in Animals

Pathogenesis – General Pathways

- Port of entry
 - initial replication sites
 - vital organs (e.g. spleen, liver and brain)
 - damaged directly via viral lysis
 - or indirectly via immuno-pathological reactions
 - or recovery via specific (Abs)
 - or unspecific immune responses
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Pathogenesis – Viral Spread (assumed basic pattern)

- Port of entry – *resorbtive viremia*
or via lymphatic vessels
to regional lymphnodes =
 - initial replication sites – *release into circulation causing primary viremia and thus systemic infection*
 - replication in target organs – *release into circulation causing intensive (secondary) viremia*
 - Variations on species and individual level of disease manifestation
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Pathogenesis – Timeframe of Viremia

Species	Age Group	Viremia detectable	Viremia persistence
Sheep	< 1 week	16hrs after infection	whole disease period (mortality poss. after 36 – 48 hrs)
Sheep, Goats, Cattle	> 1 week	24-48hrs After infection	Up to 7 d (peak on day 2 – 5)

Viral Persistence in Spleen of Sheep up to 21 days

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Pathogenesis – Viraemic Titres

Lambs : $10^{10.1}$ MIPLD₅₀/ml

Sheep : $10^{7.6}$ MIPLD₅₀/ml

Kids : $10^{8.2}$ MIPLD₅₀/ml

Goats : $10^{5.6}$ MIPLD₅₀/ml

Calves : $10^{7.5}$ MIPLD₅₀/ml

Ponies : $10^{2.5}$ MIPLD₅₀/ml

Correspondence with degree of species susceptibility

(MIPLD = mouse intraperitoneal lethal dose)

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Pathogenesis – Species Susceptibility

- Extremely Susceptible (>70% Mortality):
e.g. lambs, kids
 - Highly Susceptible (>20%<70% Mortality):
e.g. sheep, calves
 - Moderately Susceptible (<10% Mortality)
e.g. adult cattle, goats, African Buffalo, Humans
 - Resistant (benign/inapparent infection):
e.g. equines, pigs, carnivores
 - Refractory (no infection):
birds, reptiles, amphibiae
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Pathogenesis – Disease Forms

- Extremely Susceptible Hosts (young lambs and kids) :
peracute hepatic disease
 - Highly (Sheep, Calves) and Moderately Susceptible Hosts (e.g. Cattle, Goats):
mostly benign infection
various percentage of severe hepatic disease
 - Encephalitic Form in ruminants reported only from artificial, but not natural infection (immunopathological mechanisms discussed for encephalitic manifestation in rats and humans) but viral infection of brain of aborted fetus; CNS anomalies (porencephaly, hydrancephaly and microencephaly) reported after usage of Smithburn strain vaccine in ewes
 - Ocular lesions not reported in animals
 - Abortions: - due to febrile disease of dam or
- due to foetal infection and death (majority)
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Pathogenesis – Organ/Tissue Preferences

- In Vitro: replication in almost all cell types (except e.g. primary macrophages; but macrophages infected in vivo)
- In Vivo : macrophages, spleen, adrenocortical cells, hepatocytes, renal glomeruli (+some tubules), endothelial cells, brain cells with encephalitic form (e.g. rats), lung tissue

Correspondence with respective organ lesions

Major Virus Replication: Liver & Spleen

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Pathogenesis – Pathogenic Properties 1

- Direct viral cell lysis of target cells in (per-) acute form (e.g. in newborn lambs); cellhydrops, karyopyknosis etc.
 - Haemostatic derangements:
 - moderate thrombocytopenia in benign infection in sheep
 - viral hemorrhagic fever with bleedings and disseminated intravascular coagulation
 - impaired clearance of virus – widespread tissue damage causing a.o. vasculitis and hepatic necrosis as most critical lesions – hemorrhagic syndrome
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Pathogenesis – Pathogenic Properties 2

- Intravascular coagulation triggered by destruction of antithrombotic properties of endothel
 - Procoagulants released into circulation by necrosis of a.o. hepatocytes
 - Diminished production of coagulation proteins and reduced clearance of activated coagulation factors through critical liver damage – enhancement of DIC – drop of tissue perfusion – tissue damage
extensive hemorrhages and fatalities through anemia, shock and hepatorenal failure
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Pathogenesis – Abortions

- No evidence of fetal infection (?)

or

- Fetal infection and death

massive hepatic necrosis

often also infection of brain

no placentitis described (?) but virus retrievable

Septic Metritis as consequence of retained placenta due to abortion

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Pathogenesis – Host Response

- Fatal hepatic form: Host immune system overrun by virus and weakened by lymphoid necrosis
 - Recovering hosts: Macrophages (production of interferon and triggering cell-mediated immune response) and Abs (2- 3 days after infection in rats and sheep) important for early defense
 - Apparently genetic resistance inherited as simple Mendelian gene of large effect
 - Mortality rate e.g. in gerbils not determined by infectious dose
 - Apparently higher virus replication rates in hepatocytes of susceptible rat strains than in those of resistant rat strains – Difference in susceptibility on cell level (before reaction of immune system)
-

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Clinical Diagnosis

- History: Species, season, type of symptoms
- Clinical examination and signs
- Sampling live animal
- Post-Mortem
- Sampling during PM

Individual cases generally unspecific;

Key symptom: many simultaneously occurring abortions/stillbirths death of new-bornes (after heavy rains and in conjunction with human RVF disease) together with clinical disease in ruminants during epidemic.

Does not exclude cases of smaller numbers during Inter-epidemic times !

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Clinical Diagnosis – small ruminants

■ **Sheep**

new-born lambs: usually peracute course

Incubation period: 12- 36 hrs, often biphasic fever

listlessness, increased respiration (can be abdominal in final stages),

abdominal pain,

mortality: up to and more than 90% in lambs < 1week

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Clinical Diagnosis – small ruminants (Sheep)

animals >2weeks : peracute, acute (mostly) or inapparent

peracute course : sudden death without remarkable signs

acute course: Incubation period: 24- 72 hrs,

fever for 24 – 96 hrs

listlessness, increased respiration, anorexia

may have melaena or bloody/foetid diarrhoe, mucopurulent

nasal discharge, icterus (few), (unphysiological regurgitation of ingesta)

Abortions (40-100% of pregnant animals) at any gestation stage (usually autolysed fetuses)

mortality rate: 5-30%

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Clinical Diagnosis – small ruminants

■ **Goats :**

as for sheep, but reportedly regional
differences in susceptibility

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Clinical Diagnosis – large ruminants

■ **Cattle :**

calves:

similar as in lambs and kids (febrile, anorectic, diarrhoe with bloody and/or foetid character), but more cases with icterus;

fatalities 2- 8 days after infection

mortality rate: <10% , 20 % (SP), 70% (experim.)

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Clinical Diagnosis – large ruminants

- Adult Cattle: acute or inapparent (frequently)

Incubation period :

Fever for 24- 96 hrs

Anorexia, bloody/foetid diarrhoe, weakness, discharge from cranial mucous membranes (lachrymation, salivation, nasal discharge), dysgalactia; icterus

Abortion often only clinical signs(15-40% during epidemics)

mortality rates : +- 10 % ; 30 % (Egypt)

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Clinical Diagnosis – large ruminants

- Other reported (unusual findings):
 - dermatitis crustosa, catarrhal and erosive stomatitis, coronitis, laminitis, exungulation (suspected to be primarily caused by concurrent infections, e.g. BT)
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Clinical Diagnosis – Abortions Ruminants

- due to febrile reaction or infection of fetus
 - during all stages of gestation
 - usually autolysis of aborted fetus
 - fertility afterwards appears not be affected, if not complications due to retained placenta, purulent metritis and salpingitis
-

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Morbidity, Mortality and Abortion % (Lit.)

Species	Age Gr.	Morbidity	Mortality	Abortions
Sheep	newborn		+ - 90 %	NA
	>2weeks		5- 30 % (SA)	40-100 % (SA)
			60 % (Eg. '77)	80-100 % (Eg'77)
Goats	all	as sheep (SP)	as sheep (SP)	as sheep (SP)
		0 % (Eg. '77)	0 % (Eg. '77)	0 % (Eg. '77)
			<50% (Su. '73)	100 % (Mau.'87)
Cattle	calves		<10% (SP)	
	calves		70% (experim.)	
	all (adult)		20 % (SP); 30% (Eg.'77)	15- 20 % (SP)

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RVF Outbreak 2008 Ehlanzeni – Observations and Calculations

- **Grootboom**

40 % seropositives (6/15 tested)

- **Vygeboom**

53 % seropositives (6/15 tested)

- **One Tree Hill**

1.6 % abortions (2/121 pregnant cows)
(owner vaccinated before serosurvey)

- **Richtershoek**

8% mortality (4/51); all < 2yrs

bad overall condition, diarrhoe

PM: icterus, swollen livers with mottled appearance

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RVF Outbreak 2008 Ehlanzeni – Observations and Calculations

- **Blinkwater:**

- 31 % seropositives (31/100)

- 14 % abortions (6/43)

- + - 5 % morbidity and mortality*

- **Hoggelegen:**

- 42 % seropositive (3/7)

- 50 % abortions (2/4 previously pregnant animals)

- Morbidity (abortions): 28 % (2/7)

- Mortality : 0 %

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Epidemiological figures- Afr. Buffalo

Before Outbreak in DFBBP in Nkomazi area 2008:

371 buffalo (317 in bomas, 160 being adult cows) in the project at DFBBP in Nkomazi :

- 3 bulls, 11 cows and 1 calf in the TB positive;
- 5 bulls, 24 cows, 82 subadults and 4 calves in the TB suspect;
- 20 bulls, 126 cows and 27 calves in the TB free bomas;
- 14 calves in the hand-rear bomas;
- 54 buffalo in field camp

Results of RVF Outbreak:

- one adult female buffalo died from RVF on 14 January 2008
 - very young calf died from or while suffering from RVF on 25 January 2008
 - eight adult female buffalo aborted due to RVF from 27 January to 28 February 2008.
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Epidemiological figures- Afr. Buffalo

- Outbreak in DFBBP in Nkomazi area 2008:
- Morbidity (fatal cases and abortions) : 2.6 % (including buffalo in camp)
- Morbidity (fatal cases and abortions) : 3.1 % (excluding buffalo in field camp)
- Mortality (excluding abortions) : 0.5 % (including buffalo in field camp)
- Mortality (excluding abortions) : 0.6 % (excluding buffalo in field camp)
- Abortions : 6.8 %

8/117 over 33 days in January and February 2008 due to RVF (average inter-calving period in the buffalo project was determined at 462 days (1999-2007, n = 756), implying an average pregnancy prevalence of 73%, and thus 117 cows being pregnant pregnant at the onset of the outbreak out of total of 160)

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Epidemiological figures- Afr. Buffalo

Outbreak in DFBBP in Nkomazi area 2008:

Perinatal mortality rates (2002-2007, Jan. 2008):

<i>Bomas</i>	<i>Abortion</i>	<i>Stillbirth</i>	<i>Neonatal death (<5w)</i>
TB free	0 – 3 % 0%	0 – 4 % 13%#	0 – 10 % 13%
TB suspect	0 – 9%* 57%@	0 – 10%* 0%	0 – 10% 14%@
TB positive	0 – 18%* 0%	0 – 9%* 0%	0 – 18% 0%

* enhanced by Brucellosis infection until 2007

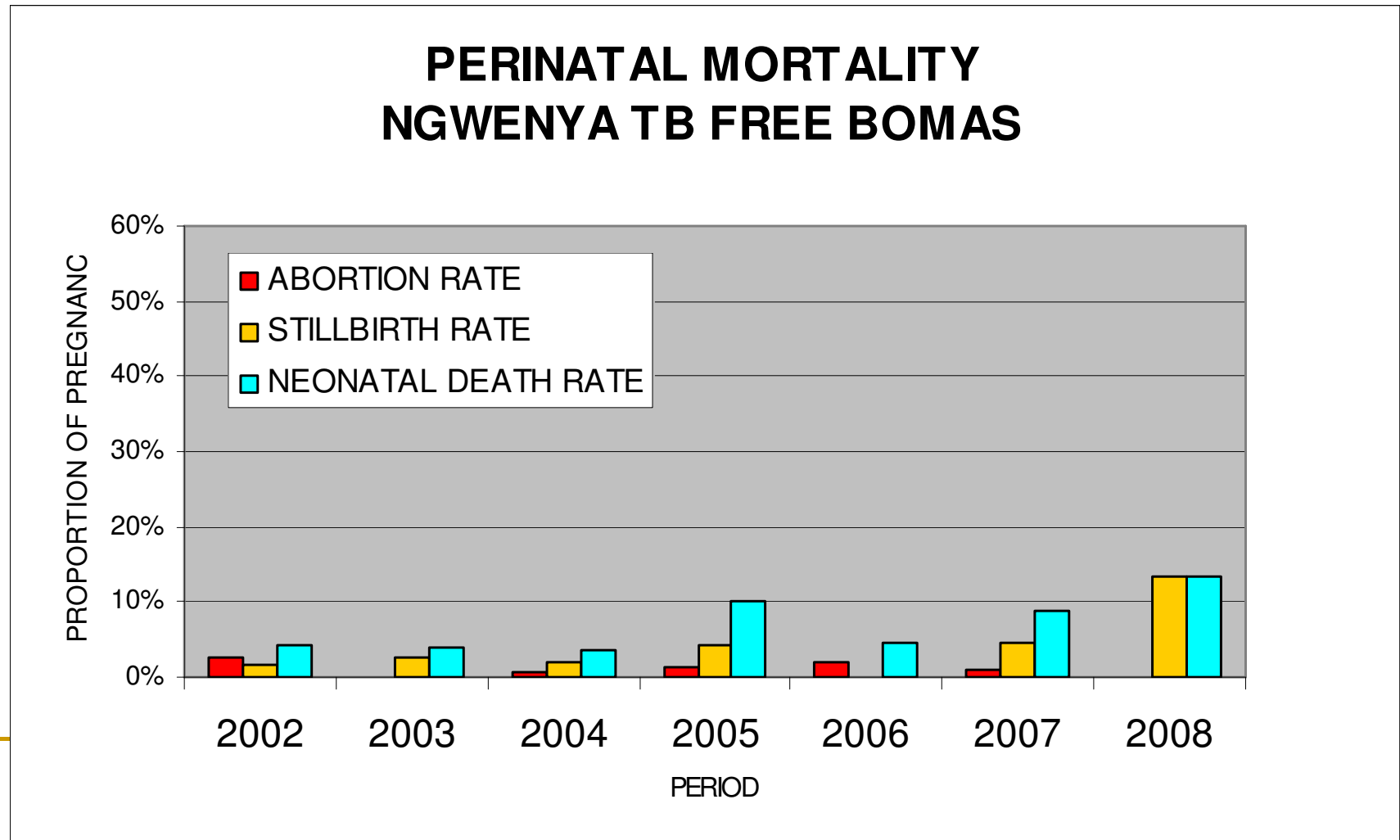
same boma !

@ RVF (abortions: 3/4 confirmed; neonatal 1/1 confirmed)

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Epidemiological figures- Afr. Buffalo

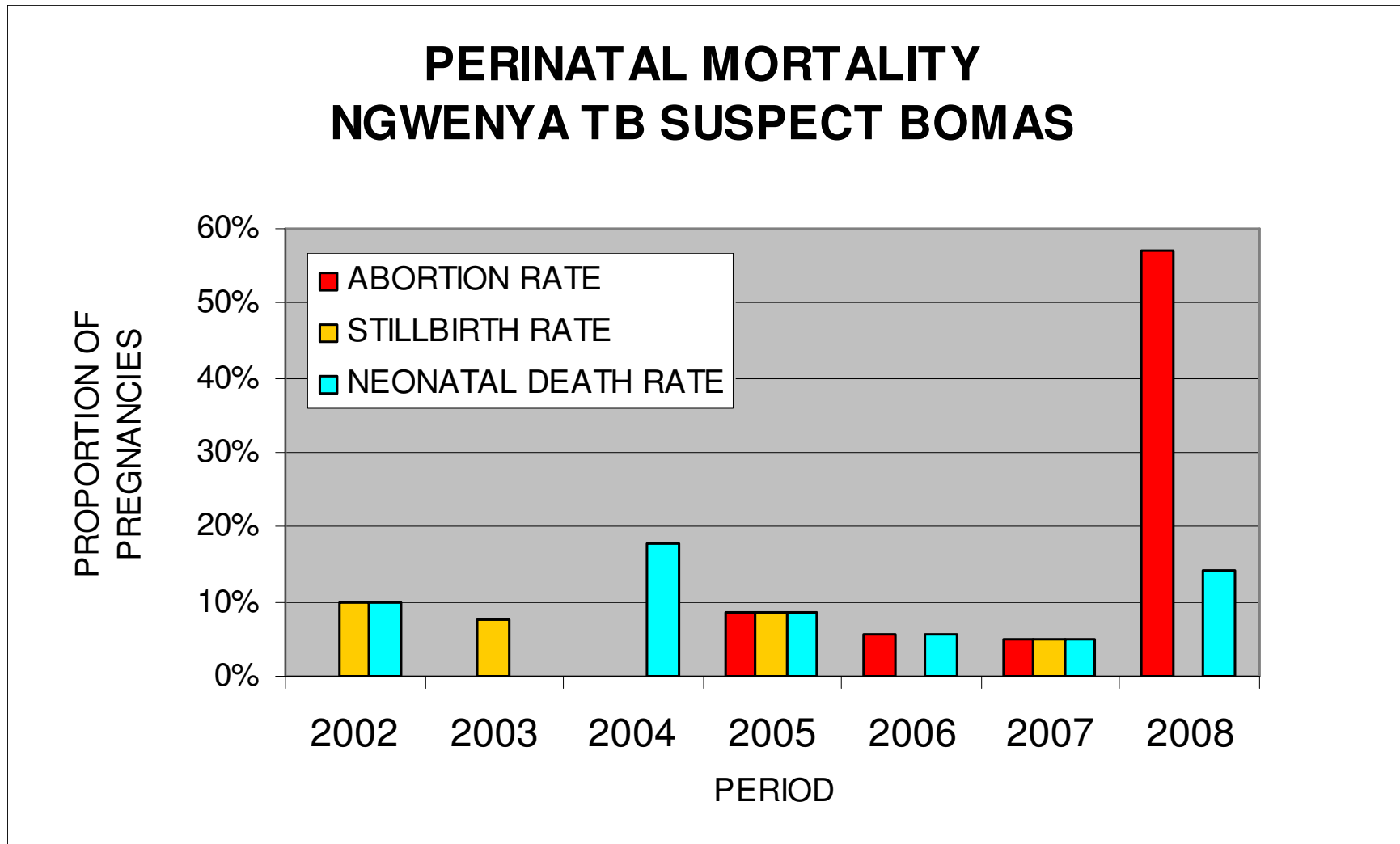
Outbreak in DFBBP in Nkomazi area 2008:



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Epidemiological figures- Afr. Buffalo

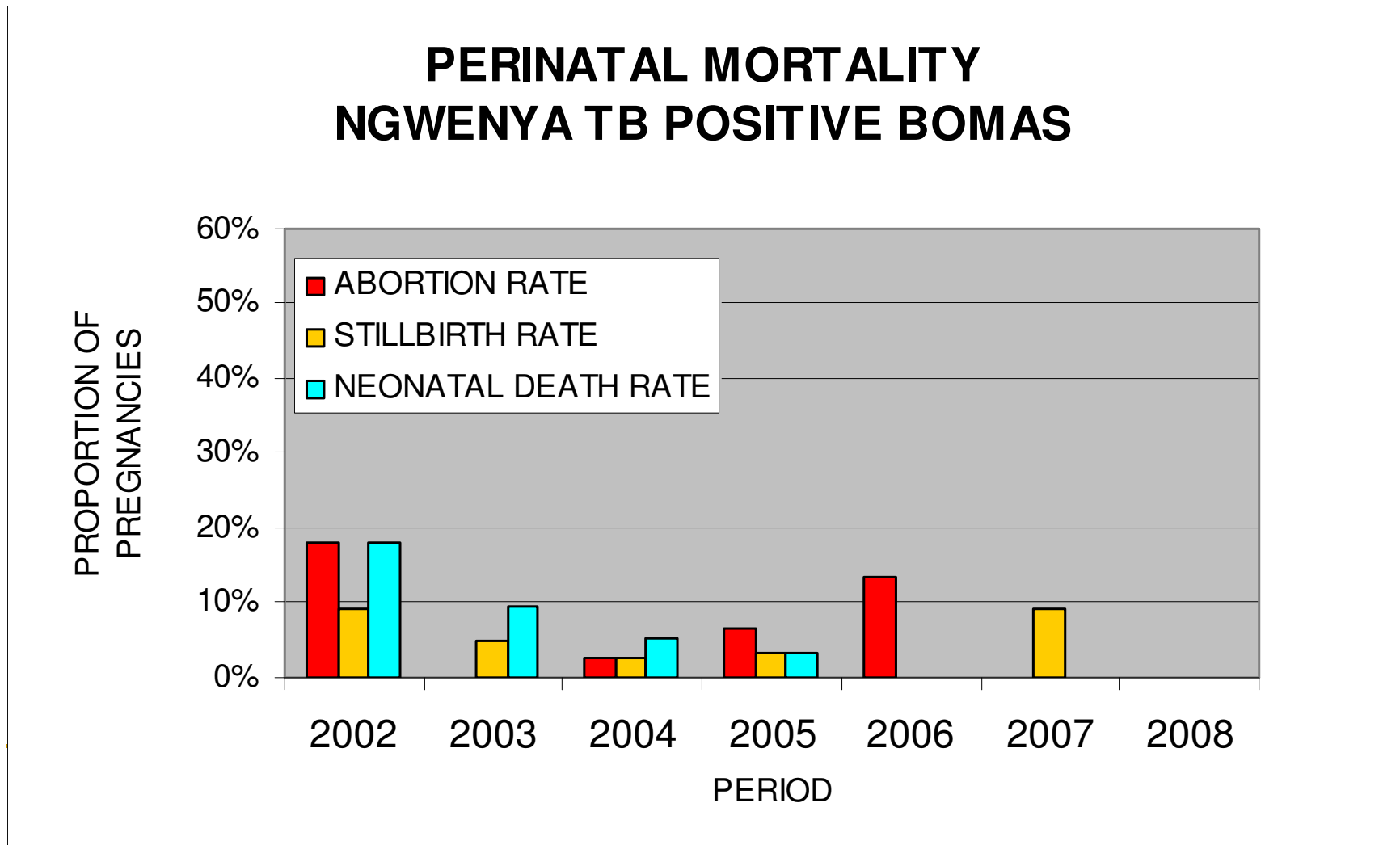
Outbreak in DFBBP in Nkomazi area 2008:



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Epidemiological figures- Afr. Buffalo

Outbreak in DFBBP in Nkomazi area 2008:



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Epidemiological figures- Afr. Buffalo

Outbreak in DFBBP in Nkomazi area 2008:

Seropositives:

- 9/16 calves (56%); 7-9 months old, 1st stage quarantine
 - weaned at 5 months of age : 8/11 (72%) seroconverted when 7-9 months old
 - handreared : 1/5 (20% seroconverted)
 - 8/18 calves (44%) in hand rearing facility seroconverted
 - 6 month old : 33 % seroconversion
 - 3 month old calves : 40 % seroconversion
 - 1 month old calves : 50 % seroconversion
-

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Epidemiological figures- Afr. Buffalo

Outbreak in DFBBP in Nkomazi area 2008:

TB Suspect bomas :

- 12/19 adults (61 %) seroconversion All four cows which aborted were seropositive (highest titres of all : 57, 59, 69 and 96)
 - 2 bomas with abortions : 91% and 60% seroprevalences
 - 2 bomas with no abortions : 40% and 29% seroprevalences
 - 6 calvings after vaccinations (pregnant animals with inactivated, others with live attenuated vaccine):
 - 3x negative titres, 2 x borderline positive titres of 10 and 1 x positive titre of 44
-

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Epidemiological figures- Afr. Buffalo

Outbreak in DFBBP in Nkomazi area 2008:

TB positive bomas :

- 6/13 adults (46%) Both cows which aborted were seropositive with titres of 22 and 52.
- boma with abortions : 75% seroprevalence
- boma with no abortions : 0% seroprevalence
- 3 calvings after vaccinations (pregnant animals with inactivated, others with live attenuated vaccine):
- 3 x negative titres
-



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Epidemiological figures- Afr. Buffalo

Outbreak in DFBBP in Nkomazi area 2008:

TB free bomas :

- 40/124 cows (32 %)
 - 3/19 bulls (16%)
 - 21/ 26 unweaned calves (81%)
 - 64/169 animals (38%) Both cows which aborted had high positive titres of 77 and 82
 - 2 bomas with abortions: 27% and 31% *seroprevalence*
 - One boma : 0% seroprevalence
 - Other 15 bomas: 8 – 73 % seroprevalence
 - 34 calvings after vaccinations (pregnant animals with inactivated, others with live attenuated vaccine):
 - Including 6 x positive titres
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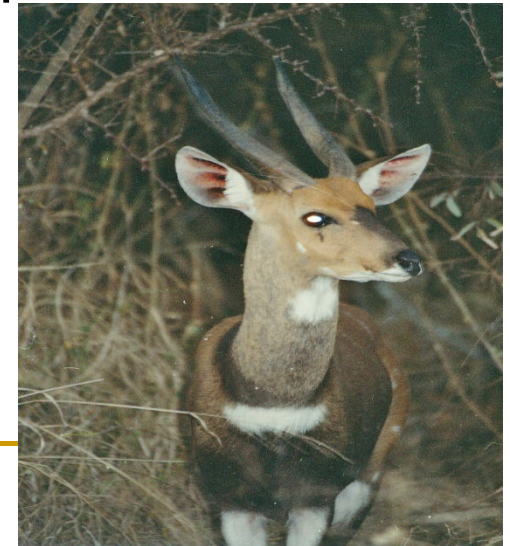
RVF in Wild Animals

Species with documented positive serology:

a.o. African buffalo, black and white rhino lesser kudu, impala, African elephant, kongoni, waterbuck, gerenuk, eland

Clinical manifestations under natural conditions speculated

Intraspecific differences in susceptibility linked to environment and fitness (e.g. Afr. Buffalo) ?



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Clinical Chemistry

- marked leukopenia first 3 to 4 days of infection (even in benign infections), simultaneously with viremia and fever peak can be picked up as additional finding on BS
 - marked increases in the serum concentrations of some liver enzyme (sorbitol dehydrogenase, glutamate dehydrogenase, aspartat aminotransferas)
little practical value in routine field vet scenario
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Pathology (Macroscopical changes)

Hepatic lesions (variance according to age): hepatomegaly, focal necrosis, subcapsular hemorrhages, congested patches

Fibrinous perihepatitis; edema and hemorrhages in gall bladder wall, blood-tinged bile

Icterus

Hemorrhages in abomasum with dark luminal content (new born lambs); blood in intestinal lumen (adult sheep and cattle)

Splenomegaly, marginal infarcts (some)

Enlarged and edemateous lymphnodes

Disseminated haemorrhages (sc, serosal and visceral)

Bloody effusions into body cavities

Lung oedema and congestion

Nephrosis

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Histopathology

Hepatic necrosis key characteristic finding

very extensive and diffuse in peracute cases of highly susceptible hosts, lesser degree and more focal in others

(multifocally in older sheep and calves; adult cattle 60% centrizonal necrosis, massive diffuse necrosis 30%; 10% focal necrosis)

Other findings:

Lymphoid necrosis (and depletion)

Nephrosis

Lung congestion, edema and hemorrhages

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Rift Valley Fever in Animals**

Differential Diagnosis

- **Abortion : Abortion storms**
Age and condition of aborted fetus
 - **Icterus/Liver Impairment**
 - **Diseases with seasonally focussed
appearance (and/or
movements/congregations)**
 - **Acute Deaths**
-

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Differential Diagnosis – Abortions (Cattle)

- **Brucella abortus:**

abortions around 7th to 8th month of gestation /last trimester (or weak newborns and/or retained placenta)

slightly viscous fluid with yellowish tinge between endometrium and chorion

placenta can have leathery appearance with fibrinous exudate (yellowish)

fetus: mostly s/c oedema, effusions in body cavities; purulent/fibrinous bronchopneumonia; **content of abomasum lemon coloured with flakes**

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Differential Diagnosis – Abortions (Cattle)

■ **Campylobacter fetus ssp. venerealis:**

abortions around 5th to 6th month of gestation / second trimester (or premature/weak calves)

cotyledones often edematous, yellowish tinge, partly necrotic, brown exsudate

often accompanying catarrhalic vaginitis, cervicitis and endometritis

fetus : sc/ edema, effusion in body cavities, liver necrosis

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Differential Diagnosis – Abortions (Cattle)

■ **Listeria monocytogenes:**

abortions around 7th to 8th month / last trimester (also premature and or weak calves)

often retained placenta, endometritis and septicaemia

(History with abnormalities in food ?)

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Differential Diagnosis – Abortions (Cattle)

- **Leptospirosis (L pomona, hardjo etc.):**
abortions after 6th month of gestation
atonic and yellowish cotyledones
amnion and allantochorion edematous
fetus: hemorrhagic effusions in body cavities,
inflammatory changes in kidneys
-

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Differential Diagnosis – Abortions (Cattle)

■ **Chlamydia psitacci:**

abortions around 6th to 8th month of gestation
(last trimester)

placenta normal or necrotic (also hyperplastic
placentitis)

fetus: s/c edema, ascites, petechiation of
esophagus and traches, liver degeneration

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Differential Diagnosis – Abortions (Cattle)

■ **Trichomonas fetus:**

Abortions around 2nd to 4th month of gestation

Often early death of fetus with partial

maceration

thin, **greyish fluid with purulent flakes**

characteristic

The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of
Rift Valley Fever in Animals

Diff. Diagnosis – Abortions (L. and S. rum.)

■ **Fungal abortions (e.g. *Aspergillus*,
Absidia, *Mukor*, *Rhizopus* etc.):**

Abortions mainly around 3rd to 7th month of
gestation

mostly diphteroid/necrotic placenta

fetus: sometimes focally mycotic dermatitis

The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of Rift Valley Fever in Animals

Diff. Diagnosis – Abortions (L. and S. rum.)

- **Wesselsbron Disease (WSL):**

also arthropod- borne virus – clusters with same climatic/seasonal conditions

mortalities in young ruminants

abortions in ewes (never from field), but

RVF with much higher percentages of mortality and abortion

WSL is less acute, causes less extensive liver lesions, regularly icterus

As with RVF: haemorrhages from mucus and free blood in abomasum (dark brown if partially digested)

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Diff. Diagnosis – Abortions (Cattle)

■ **Other viral:**

BHV 1 (5th to 6th month; necrotic placentitis,
multiple focal necrosis in liver of fetus)

BVD

Bluetongue

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Rift Valley Fever in Animals**

Differential Diagnosis – Abortions (Cattle)

■ **Other bacterial:**

Haemophilus somnus (sporadic abortions)

Yersinia pseudotuberculosis (last trimester)

Salmonella spp

A pyogenes

Mycoplasma

Coxiella burnetti

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Differential Diagnosis – Abortions (Cattle)

- Other: Parasites, e.g.
 - Sarcocystis cruzei
 - Babesiosis
 - Neospora caninum
 - Hammondia pardalis
-

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Differential Diagnosis – Abortions (S. ruminants)

- **Brucella ovis:**

only affects sheep, abortions in last trimester, changes similar as with *B. abortus* in cattle

- **Brucella melitensis:**

mainly goats, rarely sheep and cattle
abortions in last trimester

changes similar as with *B. abortus* in cattle

Dams often with fever, weight loss, diarrhoea, mastitis and lameness

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Differential Diagnosis – Abortions (S. ruminants)

■ **Salmonella abortus and dublin:**

abortions in last six weeks of pregnancy or
weak new-borns

hemorrhagic-purulent, partly diphtheroid-
necrotic placentitis

allantochorion edematous, necrotic and
hemorrhagic

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Differential Diagnosis – Abortions (S. ruminants)

- **Listeria monocytogenes:**
abortions in last trimester, similar as in cattle
 - **Campylobacter fetus ssp. intestinales:**
last two months of gestation, similar as in
cattlee
 - **Yersinia pseudotuberculosis:**
abortions at end of pregnancy
-

The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of
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Differential Diagnosis – Abortions (S. ruminants)

■ **Chlamydia psitacci:**

abortions in last 2 – 3 weeks of gestation

placenta either normal or with focal or diffuse
diphtheroid-necrotic inflammations

fetus: s/c edema, effusion in body cavities,
multiple petechiation

■ **Coxiella Burnetti:**

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Differential Diagnosis – Abortions (S. ruminants)

■ **Other viral:**

Border Disease

WSL (Wesselsbron Disease)

Bluetongue

Akabane Virus

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Differential Diagnosis – Abortions (S. ruminants)

■ **Toxoplasma gondii:**

abortions at end of gestation

kotyledones reddish, edematous, multiple
necrotic foci

fetus: mostly NAD

■ **Other parasites:**

Sarcosporidia, Neospora caninum

**The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of
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Differential Diagnosis – Hepatopathy

- **Poisonous plants**
 - **Bacterial Septicemias**
 - **Protozoons**
-

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Differential Diagnosis – Other symptoms

- Rinderpest
 - Peste De Petits Ruminants
 - Nairobi Sheep Disease
-

The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of Rift Valley Fever in Animals

Pathological Findings in Abortions of African Buffalo

The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of Rift Valley Fever in Animals- Abortions in Captive African Buffalo

Male fetus +/- 10 months



The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of Rift Valley Fever in Animals- Abortions in Captive African Buffalo

Female fetus +/- 11 months



The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of Rift Valley Fever in Animals- Abortions in Captive African Buffalo

Female fetus +/- 11 months- Exungulation



The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of Rift Valley Fever in Animals- Abortions in Captive African Buffalo

Female fetus +/- 11 months- Decomposition



The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of Rift Valley Fever in Animals- Abortions in Captive African Buffalo

Female fetus +/- 4 months



The Pathogenesis, Clinical Diagnosis and Differential Diagnosis of Rift Valley Fever in Animals- Abortions in Captive African Buffalo

Female stillbirth, dystocia

