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The Use of Antibiotics in Broodmares With Post-service Endometritis

A Knowledge Summary by

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Clinical bottom line

There is currently a lack of evidence to suggest that antibiotics delivered into the uterus post-service improves pregnancy rates. The evidence does support that post-service treatment with or without antibiotics improves pregnancy rates in mares with endometritis compared to no treatment (pregnancy rates between 40-90% compared to 0-56% respectively). The studies further identify the need to recognise mares at risk of post-service endometritis to target appropriate therapy.

Question

In broodmares with post-service endometritis after natural cover, is antibiotic intervention superior to other routine therapies without antibiotic intervention in increasing pregnancy rates?

Clinical Scenario

It is well recognised that endometritis decreases pregnancy rates (Le Blanc and Cause 2009). However, there is no clear definition of post-service endometritis (Le Blanc and Cause 2009). When mares are presented post-service, and suspected to have endometritis a decision is required by the clinician to use or not use antibiotics in combination with other routine therapies such as uterine flushing and ecboic agents. It is often unknown when the clinician is making an assessment if the endometritis is infectious or sterile in origin and mares are currently recommended to be treated with antibiotics regardless of cause (Morel 2003; Blanchard *et.al.*, 2000). The use of antibiotics should be evidence-based to minimise the risk of microbial resistance and opportunist fungal infections (Assad *et.al.* 2015).

The Evidence

Seven publications were identified in the literature searches. These comprised 2 descriptive studies, 1 observational study, 2 randomised non-blinded controlled trials and 2 non-randomised non-blinded controlled trials. Included publications were of level 3 (randomised control trials) or level 4 (lower quality controlled trial) (OCEBM Levels of Evidence Working Group). The outcomes studied varied between the studies including pregnancy rates at 15 days (Pycock and Newcombe 1996; Gores-Lindholm *et.al.* 2013; Sharma *et.al.* 2011), 45 days (El-Roos 2004), 60 days (Noseir 2002; Taha 2007), or unknown (Pascoe 1990). Further, there was no standard population treated, antibiotic prescribed or method of administration between the studies.

In the three studies with no case selection any treatment was seen to benefit pregnancy rates over no treatment at all (Pycock and Newcombe 1996; Pascoe 1990; El-Roos 2004). This is similar to mares with a previous history of endometritis with a significantly higher pregnancy rate in mares treated with antibiotics and ecboic agents compared to no treatment at all (Noseir 2002; Taha 2007). In the two studies which compared mares with and without signs of endometritis and treatment with antibiotics, higher pregnancy rates were achieved in mares that were not treated and had no signs of endometritis (Sharma *et al.*, 2011; Gores-Lindholm *et.al.*, 2013). The findings support the need for case selection in treating mares with post-service induced endometritis.

Summary of the evidence

Pycock (1996)	
Population:	574 Thoroughbreds, 647 hunters (crossbreds) and 46 pony types with ages ranging from 3-22 years and mixed reproductive status (maiden, barren, post-parturient)
Sample size:	n = 1267
Intervention details:	Mares were assigned in rotation to one of four treatment groups. Group 1: no treatment (n=322) Group 2: intrauterine antibiotic treatment within 72 hours of mating (1200mg procaine penicillin combined with 1500mg dihydrostreptomycin and 900mgs framycetin made to a volume of 12 mls or neomycin (1g) polymyxin B (40,000 iu) and furaltadone (600mg) with crystalline benzylpenicillin (3g). (n=317) Group 3: oxytocin (25 iu) administered by IV injection within 72 hours of mating (n=316) Group 4: oxytocin (25 iu) administered IV followed 30mins later by intrauterine antibiotics as described for group 2 within 72 hours after mating (n=314)
Study design:	Prospective non-blinded, non-randomised controlled- trial
Outcome studied:	Ultrasound pregnancy detection on day 13, 14, or 15 post ovulation and repeat examination between 27-30 days after ovulation. Early embryonic death rate determined by the presence of a vesicle at first scan and absence at second scan
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> - Any treatment (oxytocin alone or in combination with intrauterine antibiotics) significantly increased pregnancy rates over untreated control mare (control pregnancy rate 56%) - No difference in pregnancy rates between group 2 (intrauterine antibiotics) (64%) and group 3 (oxytocin) mares (63%) - Mares in group 4 (intrauterine antibiotics and oxytocin) had higher pregnancy rates than mares in group 2 and group 3 (group 4 pregnancy rate 72%) - No difference in early embryonic loss between treatment groups
Limitations:	<ul style="list-style-type: none"> - Mares were not subject to any diagnostic procedure to confirm the presence or absence of infection prior to antibiotic treatment - There was no data pertaining to presence of clinical or subclinical signs of endometritis such as intraluminal fluid within the groups prior to treatment - Unknown spread of ages and reproductive status (barren, maiden, post-parturient) within groups - Unknown if mares were selected at foal heat or recruited to the study after multiple mating attempts during the season

Pascoe (1990)	
Population:	Unknown population of foaling mares bred on foal heat, short cycled and bred at 18 days or bred after 30 days
Sample size:	n = 1090
Intervention details:	Mares were treated post ovulation with plasma and intrauterine antibiotic (n=420 composed of foal heat n=240; short cycled n=100; and bred after 30 days n=80), intrauterine antibiotic alone (n= 450 composed of foal heat n=240; short cycled n=100; and bred after 30 days n=110) or control no treatment (n= 220 composed of foal heat n=120; short cycled n=50; and bred after 30 days n=50). (Antibiotic used was 6 million IU procaine penicillin and 4gm neomycin sulphate)
Study design:	Observational study
Outcome studied:	Conception rate (unknown determination)
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> - In mares that were short cycled plasma and antibiotic infusion increased conception rates by 30% compared to mares that had no treatment. - Mares bred on foal heat had higher conception rates when treated with plasma and antibiotic infusion (74%) or antibiotic infusion (64%) alone, than no treatment (52%)
Limitations:	<ul style="list-style-type: none"> - The population of mares within groups regarding age, reproductive status, previous endometritis and breed is unknown. - No statistical analysis was performed to determine the significance of the findings - No data regarding signs of clinical or subclinical endometritis within the groups

Taya (2007)	
Population:	Arabian maiden mares ranging from 4 to 8 years with a diagnosis of persistent mating induced endometritis. Mares were determined to have persistent mating induced endometritis if they met one of 3 criteria: <ul style="list-style-type: none"> - A history of repeat breeding (more than 3 natural services and no signs of pregnancy) - Intrauterine fluid present one/two days after breeding or - Endometrial cytology showing >5% PMN cells
Sample size:	n = 42
Intervention details:	Mares 6 hours after breeding received a uterine lavage with antibiotics (n=36). 8 hours after breeding mares were divided into 3 groups (n=12 in each group) and received either prostaglandin (250ug cloprostenol SC), or oxytocin (20 I.U IM), or no treatment. Control mares (n=6) received no treatment. Uterine lavage was performed with 500ml N-saline containing 4 million IU of crystalline penicillin and 4g streptomycin sulphate

Study design:	Prospective, randomised, non-blinded controlled trial
Outcome studied:	Pregnancy rate after 2 months of treatment
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> - There was a significantly higher pregnancy rate in mares that had a uterine lavage containing antibiotics and an injection of prostaglandin (83.3%) compared to other treatment groups - There was no difference in pregnancy rates between mares receiving antibiotic lavage alone (50%) or combined with oxytocin (66.6%) - All treatments significantly increased pregnancy rates over control (untreated) mares (0%)
Limitations:	<ul style="list-style-type: none"> - No comparison was made to treatment without antibiotics such as oxytocin alone - No description of how randomisation was performed and if mares were randomised based on criteria for selection into the study between treatment groups - Unusual antibiotic delivery through lavage system and unusual cytology performed from antibiotic flush - No cytology or culture performed prior to antibiotic lavage - No evidence of other complicating factors such as presence of fluid or uterine oedema

Gores-Lindholm (2013)	
Population:	Mares aged 4-24 years majority thoroughbred (3 standard bred and 1 quarter horse)
Sample size:	n = 154
Intervention details:	<p>Mares were client owned and divided into groups based on endometrial swab and culture results obtained pre-breeding.</p> <p>Group 1 (n=44): repeat breeders that had clinical findings suggestive of mucus over-secretion with no evidence of bacterial infection from culture of uterine lavage fluids. Mares were treated with N-acetylcysteine (NAC) 24-36 hours prior to cover followed by oxytocin (20 iu IM) 4-8 hours after infusion</p> <p>Group 2 (n=85): control group of reproductively normal mares presented on their first cycle showing no evidence of infection or inflammation on swab and cytology and intra-uterine fluid <5mm</p> <p>Group 3 (n=25): mares that had previous positive uterine cultures treated with lavage and antibiotics on previous cycle and no evidence of mucus over-secretion, intrauterine fluid >1cm</p> <p>Mares within these groups were additionally treated with intrauterine antibiotics (1g ceftiofur) dependent on previous history and farm management preferences.</p>
Study design:	Descriptive study
Outcome studied:	First cycle pregnancy rate between 13 and 15 days
Main findings: (relevant to PICO question):	<ul style="list-style-type: none"> - In mares that were suggestive to have mucous over secretion (group 1) there was no significant difference in first cycle pregnancy rates between mares receiving antibiotics and NAC and

	<p>those not receiving antibiotics (80% and 71% respectively)</p> <ul style="list-style-type: none"> - Similarly, in mares that had previously been treated for endometritis (group 3) there was no significant difference in pregnancy rates between mares treated with lavage and oxytocin, and lavage, oxytocin and antibiotics (50% and 62% respectively) - In mares with no history of endometritis (group 2) the pregnancy rate was higher for mares that were lavaged with LRS and given oxytocin (89%) than those additionally treated with antibiotics (60%)
Limitations:	<ul style="list-style-type: none"> - The study was aimed at assessing the potential for NAC to be used to clear mucous and was not comparing antibiotics as post-service treatment - The study was not blinded and it is not possible to tell why antibiotics were used or not used - Mares that previously swabbed clean may have been better identified with a low-volume lavage than uterine swab - No separation of mare age or status - In group 2 mares that had no evidence of infection, 80% of those treated with antibiotics had greater than 1cm of fluid or marked oedema 18-24 hours post-mating. There was only 18% of mares with greater than >1cm of fluid in mares treated with LRS and oxytocin alone

Noseir (2002)	
Population:	Thoroughbred mares aged 10-15 years with a history of recurrent and persistent endometritis
Sample size:	n = 36
Intervention details:	<p>Mares were assigned into 4 treatment groups post-mating (9 horses in each)</p> <p>Group 1: untreated control</p> <p>Group 2: intrauterine infusion of antibiotics (1200mg procaine penicillin with 1500 mg dihydrostreptomycin, and 1500mg gentamicin made up to 20mls)</p> <p>Group 3: single intravenous injection 4-12 hours post-mating of oxytocin (20iu)</p> <p>Group 4: intrauterine infusion of antibiotics and subsequently injected with oxytocin intravenously 30mins later</p>
Study design:	Prospective, non-blinded, non-randomised, controlled trial
Outcome studied:	Pregnancy rates at 60 days post mating either by palpation or rectal ultrasound
Main findings: (relevant to PICO question):	There was no significant difference in pregnancy rates between mares receiving intrauterine antibiotics alone (57.3%) or oxytocin administration alone (52.5%). There was, however, a significantly higher pregnancy rate between mares receiving antibiotics combined with oxytocin (67.8%) compared to other treatment groups. There was a significantly higher pregnancy rate in all treatment groups compared to the control (22.5%).

Limitations:	<ul style="list-style-type: none"> - Small sample size and low power - No definition given of recurrent and persistent endometritis - No evaluation of contributing factors such as mare status barren or rested - No available data on changes to early embryonic loss with late pregnancy diagnosis - A higher proportion of mares that received no treatment had between 6mm and 20mm of fluid (7 mares) compared to mares that were treated with antibiotics and oxytocin (3 mares) - No evidence of assessment of underlying bacterial endometritis from swab or culture results prior to cover
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El-Roos (2003)	
Population:	Native bred mares both barren and lactating
Sample size:	n = 115 (60 barren and 55 lactating)
Intervention details:	<p>Post-breeding mares were randomly assigned into 9 treatment groups.</p> <p>Group 1: no treatment (control) (n=13, 7 barren, 6 lactating)</p> <p>Group 2: intrauterine infusion of 120mls of homologues plasma (n=15, 7 barren, 8 lactating)</p> <p>Group 3: intrauterine infusion of leukocyte enriched plasma (n=14, 7 barren, 7 lactating)</p> <p>Group 4: intrauterine infusion of antibiotics (5x10⁶ IU procaine penicillin and 2g streptomycin sulphate) (n=11, 6 barren, 5 lactating)</p> <p>Group 5: intrauterine infusion of plasma and antibiotics (n=12, 6 barren, 6 lactating)</p> <p>Group 6: intrauterine infusion of antibiotics and leukocyte enriched homologous plasma (n=13, 7 barren, 6 lactating)</p> <p>Group 7: intravenous injection with oxytocin at 0, 12, and 16 hours post breeding (n=11, 6 barren, 5 lactating)</p> <p>Group 8: intrauterine infusion with homologous plasma and intravenous oxytocin given at breeding. (n=12, 6 barren, 6 lactating)</p> <p>Group 9: intrauterine infusion of leukocyte enriched homologous plasma and intravenous oxytocin given at breeding (n=14, 8 barren, 6 lactating).</p> <p>Breeding and treatment was repeated every 48 hours until ovulation was detected</p>
Study design:	Prospective, non-blinded, randomised controlled trial
Outcome studied:	Pregnancy confirmed by ultrasound at 45 days
Main findings: (relevant to PICO question):	Higher pregnancy rates were achieved with the combination of leukocyte enriched plasma and oxytocin (72%), compared to leukocyte enriched plasma and antibiotics (61%)
Limitations:	<ul style="list-style-type: none"> - Unknown randomisation method, low statistical power, and lack of statistical tests performed - Mares received double guarded swabs for culture prior to cover; however a mare with a positive culture (current endometritis) was not excluded from the trial. The distribution of mares with

	<p>endometritis prior to cover was unknown between the groups</p> <ul style="list-style-type: none"> - Unknown presence of clinical or subclinical signs of endometritis between groups - Unknown age distribution of mares and inclusion of maiden, barren and foal heat mares
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Sharma (2011)	
Population:	Thoroughbred mares in India aged from 3 years to greater than 18 years
Sample size:	N = 253 mares, (n= 1976 oestrous cycles)
Intervention details:	<p>Untreated oestrous cycles (n=1619) (control) with treated oestrous cycles (n=357) receiving either:</p> <ul style="list-style-type: none"> - intrauterine antibiotics (n=57) - uterine lavage (n=30) - oxytocin (n=55) - intrauterine antibiotics with oxytocin (n=90) - uterine lavage plus oxytocin (n=50) - intrauterine lavage plus antibiotics (n=39) - intrauterine lavage, intrauterine antibiotics, and oxytocin (n=36)
Study design:	Descriptive study
Outcome studied:	Day 16 and day 39 pregnancy rates
Main findings: (relevant to PICO question):	<p>Significantly higher ($p < 0.05$) day 39 pregnancy rates and foaling rates observed in untreated oestrous cycles (46.39%) than treated cycles (40.62%). No difference in pregnancy rates between treated oestrous cycle and untreated oestrous cycle at day 16 of pregnancy (46% and 51% respectively)</p> <p>The incidence of uterine therapies increased with increasing age</p>
Limitations:	<ul style="list-style-type: none"> - There were no criteria defined to determine which treatment option was chosen and the duration of treatment - Antibiotic choice and method of administration not discussed - Unclear at what time antibiotics were used post ovulation and if other methods were used prior to cover - No prior history of mares to determine spread of barren, maiden or foaling mares and if endometritis was present prior to cover

Appraisal, application and reflection

Post-service endometritis is a common condition and can be challenging for the clinician to diagnose and treat. Current treatment options for endometritis include intrauterine antibiotics, lavages (LRS or antibiotic infused), other uterine infusions such as mucolytics (NAC, EDTA), immune modulation treatments (plasma), and ecbolic agents (oxytocin and / or prostaglandin). The purpose of this Knowledge Summary was to evaluate the evidence comparing the use of intrauterine antibiotics in the treatment of endometritis to other routine therapies.

The diagnosis of post-service endometritis can be challenging for the clinician and varied between the studies. 4/7 studies compared treatments in mares affected by endometritis whilst the remaining studies

compared treatment in all mares. Two studies gave descriptions of how they diagnosed endometritis. Sharma et.al., (2011) and Noseir (2002) treated mares with endometritis with no definition stated. Taha (2007) defined persistent mating induced endometritis as a history of repeat breeding of more than 3 natural services without a pregnancy, intrauterine fluid one to two days after breeding, or endometrial cytology showing >5% PMN's. Gores-Lindholm et.al., (2013) diagnosed endometritis based on previous cycle uterine lavage fluid with a positive culture, repeat breeding of at least 2 cycles or 2 unsuccessful embryo transfer attempts. The lack of a consistent definition of endometritis makes comparison of treatment options challenging.

The use of controls that did not receive antibiotics was highly variable amongst the studies. The most consistent comparisons used between the studies were either no treatment or ecboic agents alone. 6/7 studies compared no treatment as a control (Pycock and Newcombe 1996; Pascoe 1990; Taha 2007; Gores-Lindholm et.al. 2013; Noseir 2002; Sharma et.al 2011), while 4/7 studies compared oxytocin at intervals ranging from 1-72 hours post mating [(Pycock and Newcombe 1996) 72 hours post mating, (Noseir 2002) 4-12 hours post mating, (El-Roos 2004) 1, 12, 16 hours post mating, (Sharma et.al. 2011) unspecified time/s]. Taya (2007) was the only study to evaluate the use of prostaglandin as an ecboic agent. Consistently it was observed that treatment of mares with endometritis improved pregnancy rates over no treatment at all (Pycock and Newcombe 1996; Pascoe 1990; Taha 2007; Gores-Lindholm et.al. 2013; Noseir 2002; Sharma et.al 2011). Ecboic agents and antibiotics had similar improvement to pregnancy rates when used alone (Pycock and Newcombe 1996; Noseir 2002). The combined effect of antibiotics and ecboic agents were seen to act in synergy and further improve pregnancy rates (Pycock and Newcombe 1996; Taya 2007; Noseir 2002).

Intrauterine antibiotics have been postulated to not only aid in the treatment of potential pathogens but also by cervical dilation enhancing fluid removal (Pycock and Newcombe 1996). The combination of oxytocin to stimulate uterine evacuation and manual dilation of the cervix has been similarly treated with the use of plasma and uterine lavages (Sharma et.al. 2011; Gores-Lindholm 2013; El-Roos 2004). Gores-Lindholm (2013) demonstrated no significant difference in pregnancy rates for mares previously treated for endometritis with lavage and oxytocin (50%) compared to lavage, oxytocin and antibiotics (62%). Similarly, Sharma et.al (2011) showed no difference in day 16 pregnancy rates in mares treated with uterine lavage and oxytocin (52%) and intra-uterine antibiotics and oxytocin (45%). While the type, volume of antibiotic and method of antibiotic installation varied between the studies, all involved uterine placement which would have led to cervical dilation.

Supporting the use of antibiotics are culture and sensitivity studies. Common bacterial isolates in endometritis include beta-haemolytic streptococcus, corynebacterium spp, and Escherichia coli (Assad et.al 2015). In all studies, the choice of antibiotic was empirical and not determined by culture and sensitivity results. Four of the studies used a combination of procaine penicillin with streptomycin, gentamicin, framomycin, and or neomycin (Pycock and Newcombe 1996; Pascoe 1990; Taha 2007; Noseir 2002) whilst one study used ceftiofur alone (Gores-Lindholm 2013). Two studies did not comment on the antibiotic used (Sharma et.al., 2011 ; El-Roos 2004), and no studies commented on the use of systemic antibiotics. Whilst the types of bacteria isolated are likely to vary geographically, Assad et.al., (2015) showed all isolates were sensitive to gentamicin and ceftriazone (100%) followed by tetracycline and chloramphenicol (92.8%). There was widespread resistance against streptomycin (92.8%) and penicillin (50%) which were commonly used in the studies. Sensitivity patterns varied based on which bacteria were isolated, with streptococcus spp having maximum sensitivity to gentamycin and tetracycline antibiotics (100%) and moderate sensitivity to penicillin (71.4%), while E. coli isolates were 100% resistant to ampicillin and streptomycin. Indiscriminate use of antibiotics has shown to increase the risk of fungal and resistant bacterial species (Assad et.al. 2015). Further use of diagnostics to identify the bacterial isolate(s) involved, and antibiotic sensitivity, may aid in the reduction of restricted antibiotics such as tetracyclines and chloramphenicol.

The outcome achieved varied between the studies, with different days of gestation considered. Majority of

the studies examined for pregnancy at 13-16 days (Sharma et. al 2011; Gores-Lindholm et.al 2013; Pycock and Newcombe 1996), whilst two studies examined only later at 45 days (El-Roos 2004), and 60 days (Taha 2007). 2/7 studies (Pycock and Newcombe 1996; Sharma et. al. 2011) commented on embryonic loss with uterine treatments by comparing pregnancy rates at 12-16 days to 28 days. There was no significant difference in embryonic loss in either study, however Pycock and Newcombe (1996) noted a higher embryonic loss when antibiotics were installed via a syringe compared to a catheter system. Early embryonic loss is estimated to be between 2.6% to 24% due to progesterone deficiency or failure of maternal recognition (Vanderwall 2008). Such that the later scanning dates in the studies by El-Roos (2004) and Taya (2007) may have had a higher negative pregnancy rate from early embryonic loss rather than failure to conceive.

Post-service endometritis is a multifactorial disease and can be challenging to manage. Currently the collective data supports the combined use of intrauterine treatments and ecbolic agents to increase pregnancy rates in mares with a history and or signs of endometritis. It is unclear if similar pregnancy results may be obtained with cervical dilation methods that do not include antibiotics in combination with ecbolic agents alone. Further, this summary identifies the need for ongoing research into defining which mares have endometritis in order to determine those that may benefit from treatment. Additional diagnostics such as culture and cytology of endometrial samples post-service could be utilised by clinicians to justify antibiotic usage. Currently clinicians should use intrauterine antibiotics judiciously as they are unlikely to improve pregnancy rates and may be detrimental to fertility in mares with no history or signs of endometritis.

Glossary

EDTA - Ethylenediaminetetraacetic acid

LRS - Lactate Ringer's solution

NAC - N-acetylcysteine

PMN - Polymorphonuclear Cell

Search Strategy	
Databases searched and dates covered:	Search terms were applied in PubMed Central accessed on NCBI website (1910-2017), CAB abstracts database accessed on OVID platform (1973-2017)
Search terms:	<p>CAB Abs</p> <ol style="list-style-type: none"> 1 (equine* or horse* or equus or equid* or mare or mares or broodmares or 'brood mares' or pony or ponies).mp. or equidae/ or equus/ or horses/ or mares/ 2 (endometritis or endometriosis or endometrial or metritis or uterine or uterus).mp. or endometritis/ or uterus/ 3 (antibiotic or antibiotics or antimicrobial or antimicrobials or anti-microbial or anti-microbials or antibacterial or antibacterials or 'antiinfective agent' or 'antiinfective agents' or 'anti-infective agent' or 'anti-infective agents' or penicillin or gentamicin).mp. or exp antibacterial agents/ or exp antibiotics/ or exp antiinfective agents/ 4 (Post-service or 'post service' or postservice or mating or induced or breeding).mp. 5 (pregnant or pregnancy or conception or conceiving or fertility or fertile or foal or foals).mp. or pregnancy/ or fertility/ 6 1 and 2 and 3 and 4 and 5 <p>PubMed</p> <ol style="list-style-type: none"> 1. equine OR horse OR mare OR mares OR broodmares OR brood mares OR pony OR ponies 2. endometritis or endometriosis or endometrial or metritis or uterine or uterus 3. antibiotic or antibiotics or antimicrobial or antimicrobials or anti-microbial or anti-microbials or antibacterial or antibacterials or 'antiinfective agent' or 'antiinfective agents' or 'anti-infective agent' or 'anti-infective agents' or penicillin or gentamicin 4. Post-service or post service or postservice or mating or induced or breeding 5. pregnant or pregnancy or conception or conceiving or fertility or fertile or foal or foals 6. 1 and 2 and 3 and 4 and 5
Dates searches performed:	March 2017

Exclusion / Inclusion Criteria	
Exclusion:	Non-English language, narrative or non-systematic review articles, unpublished data, pharmacokinetic, <i>in vitro</i> or <i>in vivo</i> experimental studies, artificial insemination protocols.
Inclusion:	Any reported use of antibiotics used in post-service treatment from natural coverings.

Search Outcome							
Database	Number of results	Excluded – non-English language publication	Excluded – non-systematic review article, conference proceeding or letter	Excluded- artificial chilled or frozen insemination	Excluded – pre-service treatment not post service	Excluded – did not answer PICO question	Total relevant papers
CAB Abstracts	53	3	15	6	2	20	7
NCBI PubMed	25	1	5	2	0	15	2
Total relevant papers when duplicates removed							7

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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